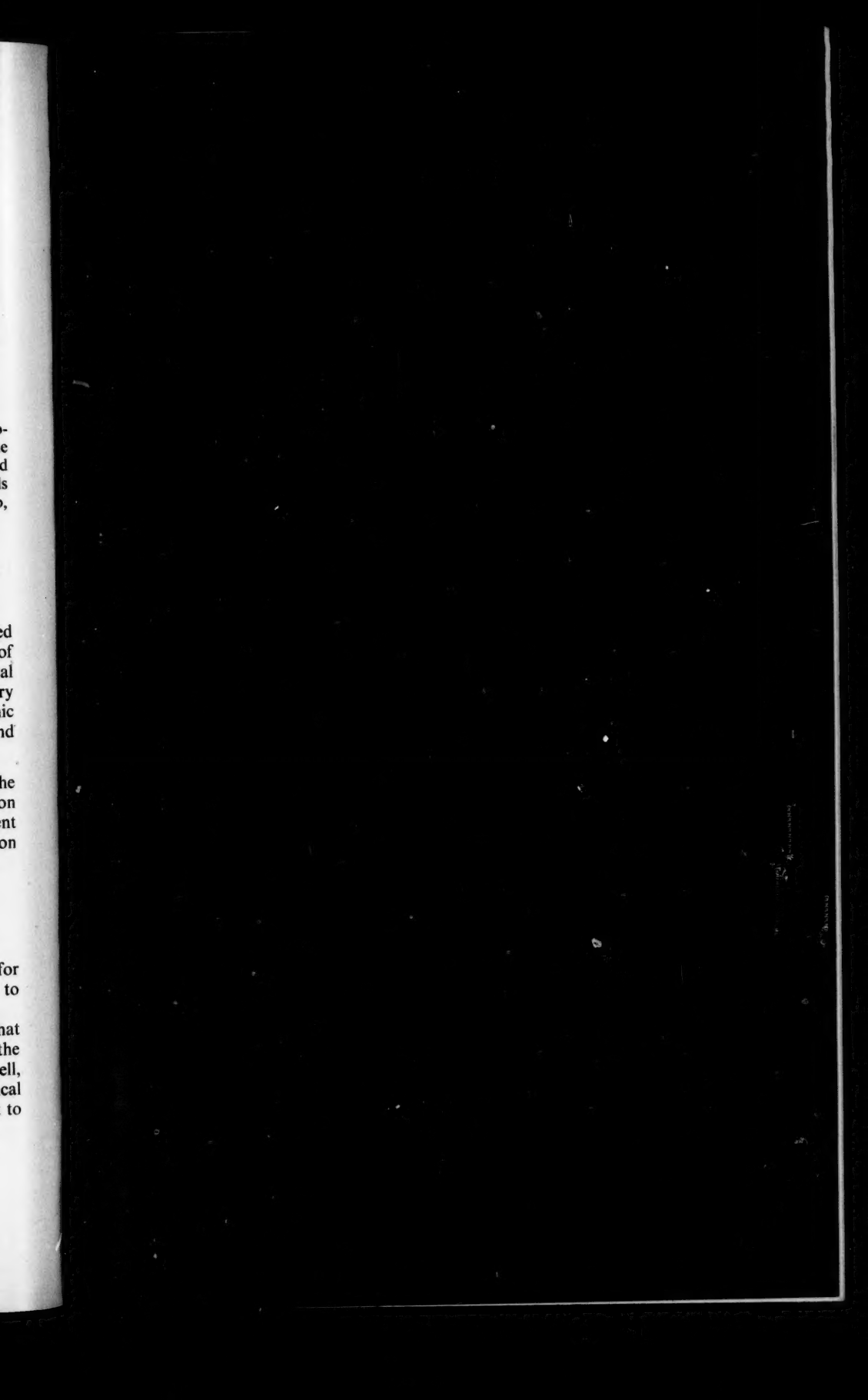

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COMMUNICATIONS

PERI-ORBITAL TUMOURS*

BY

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I FULLY realize the honour the Institute of Ophthalmology has paid me in asking me to give this address to-day. I wondered how a general surgeon could interest listeners who have devoted so much of their time to the study of ophthalmology. Many years ago I was ophthalmic house surgeon to Mr. Cargill and Mr. Lyle, and it was during that time that I first became interested in peri-orbital tumours, a subject which still is full of curiosity as far as I am concerned, and is one which embraces a wide field of pathology, coming within the spheres of the ophthalmologist, general surgeon, neurosurgeon, and dermatologist.

The commonest types of tumour around the eye are those which occur in the skin or subcutaneous tissues. The basal and squamous-cell carcinomata need little introduction, being well known by reason of their frequency, and differing pathologically in no respect from those occurring elsewhere.

RODENT ULCERS.—These grow by predilection in the skin of the lids, the supra-orbital region, both canthi, and the skin of the cheek, when compared with their incidence in other parts of the body (Figs 1 and 2). They are estimated roughly to be ten times more frequent than squamous-cell carcinomas. They arise from the deeper layers of either the epidermis or the sweat glands and present the characteristic microscopical appearance of

FIG. 1.—Rodent ulcer at the inner canthus in a man aged 68. This ulcer was excised.

* The Inaugural Lecture of the Academic Year 1951-52, delivered at the Institute of Ophthalmology, London, on October 3, 1951.

FIG. 2.—Rodent ulcer in a woman aged 88 with ulcer present for 12 years. No treatment prior to excision.

ramifying and often pointed processes which invade the dermis and subcutaneous tissue. Sometimes in microscopical sections the connection with the basal layer of the epidermis can be made out, while in others continuity with the pilo-sebaceous organs is demonstrable. The peripheral layer of cells resembles columnar epithelium, while the more central cells are irregular and contain a considerable number of mitoses. The amount of stroma is variable, being relatively large and fibrous in the more chronic type and embryonic in the more malignant ones.

Rodent ulcers tend to occur after the age of 40 years and like epitheliomata are often preceded by hypertrophic changes in the affected area of epithelium, which results in the formation of a prerodent keratosis, firmer and flatter than that of a squamous epithelioma. The reason for this predilection for the face is no doubt due to its exposure to a number of factors believed to be connected with carcinogenesis, such as trauma, and exposure to the weather and to the sun's rays, and in some cases to products of coal tar. All forms of solar or senile keratosis should be regarded with suspicion and treated as precancerous.

The natural history of a rodent ulcer varies from case to case. The first-noticed lesion may be a pimple or a small red nodule. Over a period of from 1 to 30 years the lesion grows slowly. For some years there is no ulceration, but eventually the epithelium over the lesion breaks down and, after abortive attempts at healing, a chronic ulcer remains with a heaped-up, rolled-over edge which is indurated and even hard to the touch. The clinical appearances are not always uniform. A useful classification of the different types is that by Sequeira into superficial cicatrizing, non-cicatrizing or the typical rodent ulcer, and the terebrant type with rapid spread.

TREATMENT.—This has been a subject of controversy, the choice lying between surgical excision and irradiation. Both may play a part but certain points demand consideration.

Site.—Almost all rodent ulcers can be excised, many quite simply with a margin of healthy tissue, others requiring a variety of plastic repairs including free skin grafts or flaps, but all within the scope of the general surgeon (Fig. 3). In some regions around

the eyelids surgical treatment may be difficult, but treatment by irradiation demands care to neighbouring vital structures such as the eye.

Surface Area of Lesion.—Small lesions are naturally the more readily excised, but these are also more suitable to treatment by irradiation. Skin defects left by surgical excision of large tumours are readily closed by graft or plastic repair. On occasion the cosmetic effect may be better from irradiation of large areas, but greater exposure with its attendant disadvantages is necessary.

Depth of Penetration of Lesion.—The depth of penetration is always difficult to determine accurately. The more superficial a lesion the more accessible it is to irradiation by either radium or *x*-rays. But superficial lesions are also readily treated by surgery. Surgical excision is always the treatment of choice where penetration into the bone or the tarsal plates is deep.

FIG. 3.—Large rodent ulcer which required excision and a plastic operation to cover the defect left after excision.

Age and State of Health of Patient.—Advanced age is not a contraindication to surgery. If the patient's state of health is poor, local analgesia can almost always be used.

A few additional points of contrast between surgery and irradiation may be made. Whereas one operation is required when surgery is practised and the extent of the necessary excision is gauged, for irradiation, multiple attendances are often necessary. Owing to uncertainty of depth of involvement, irradiation may fail to destroy the deeper layers of cells, and some cells may be resistant to irradiation. The peripheral extent of the growth may not be appreciated without surgical excision and thus an adequate area of tissue may not be irradiated.

The complications of surgical excision of rodent ulcers are negligible. Irradiation, however, may produce dermatitis followed by telangiectasis and atrophy or damage to vital structures such as the eye.

By surgical excision confirmation of the diagnosis is obtained. It has been shown that 13 per cent. of skin carcinomata diagnosed clinically as basal-celled epitheliomata contain prickle cells. These mixed or basal-squamous epitheliomata are more radio-resistant than pure basal-cell tumours.

Recurrences occur in about 5 per cent. of cases treated with *x* rays, but with adequate surgical excision there should be no recurrence. With regard to time lost from work, the advantage is with surgery; in many cases rodent ulcers may be treated in the Outpatient Department under local anaesthesia. With surgery there is no danger of failure to complete the treatment as there is with the repeated visits often necessary with radiation.

Lastly, in the treatment of recurrences after failure of irradiation, surgery is the only satisfactory choice, recurrence tending to be more radio-resistant than the primary growth.

PAPILLOMATA.—These may occur in the para-orbital region and if not removed are likely to become malignant. Such papillomata consist of projecting papillae undergoing proliferation and frequently branching to form secondary papillae. If the epithelium undergoes keratinization as in common

warts, these become hard and may constitute horn-like outgrowths. Haemorrhage from such a papilloma is a sign of malignant invasion and always demands radical excision. It is pathetic to see these papillomata allowed to progress towards malignant disease before radical treatment is entertained. It is surprising that members of the public will tolerate large papillomatous masses in the para-orbital region (Fig. 4).

FIG. 4.—Papilloma of the inner canthus.

FIG. 5.—Melanoma of the outer canthus.

SQUAMOUS-CELL CARCINOMATA.—Epithelioma is a new growth of squamous cells often occurring close to the lid margin in contradistinction to rodent ulcer. It infiltrates and destroys local tissue and so forms a malignant ulcer. The constituent cells are large and of irregular shape, forming a variable number of cell nests according to the grade of differentiation and therefore of malignancy. Fortunately, epitheliomata in this situation are not often of a high grade of malignancy and glandular metastases are therefore infrequent except in neglected cases. The treatment is in many respects similar to that for rodent ulcers with a choice of excision or radiotherapy. If radiotherapy is used, it is important to perform a biopsy in order that the diagnosis may be confirmed and the grading known. Surgical treatment is in many cases more satisfactory. The treatment of the lymphatic glands depends upon their clinical state when first seen and upon the age of the patient. Should they be thought to be involved, then a block dissection is considered by many at the present time to be of greater curative value, but irradiation is less disturbing to the patient, particularly in the elderly.

MALIGNANT MELANOMATA.—The third type of malignant tumour of the skin is the malignant melanoma. This may occur around the eye just as in other parts of the body. Bleeding, increase in size, or pain occurring in a previous mole are ominous signs (Fig. 5). It can hardly be stressed too often that any local interference with a pigmented naevus is dangerous for fear of stimulating actual malignant degeneration. When this has occurred no biopsy should be performed, but instead a wide excision should be made to include the tumour, a good margin of healthy tissue, and the deep fascia. These tumours are radio-resistant; they tend to spread by the lymphatics

first but also widely by the blood stream at a variable period of time after onset. Although the prognosis is generally regarded as bad a few cases live for many years, especially when adequately treated. There seems to be no way of distinguishing these and the histology is of no help.

BENIGN LESIONS.—Of benign lesions in the peri-orbital region there are only a few which call for brief attention. Simple papillomata occur frequently in the skin of the eyelids, and are formed by several layers of squamous epithelium covering a vascular stroma. Excessive keratinization forms one variety of cutaneous horn and malignant degeneration is rare. Xanthoma palpebrarum, a deposit of yellow lipoid in large polyhedral cells beneath the skin, is sometimes large enough to draw the patient's attention. Both these conditions are easily excised.

HAEMANGIOMATA.—Haemangiomata are the commonest tumours to occur in the peri-orbital region in childhood, being congenital in origin but tending to increase in size during the first few years of life. They are not, therefore, strictly tumours, with the exception of the less common hypertrophic or angio-endotheliomatous type, but congenital malformations of embryonic vaso-formative tissue. They are presented for medical attention because of the disfigurement they cause, being either of the superficial capillary type or of the deeper and more spongy cavernous type.

Superficial.—It is common knowledge that in a proportion of superficial angiomata, and particularly, in the "strawberry birthmark", spontaneous thrombosis occurs if left long enough. In order to initiate or promote this curative phenomenon a variety of procedures such as cauterization with CO_2 snow, electrocoagulation, and irradiation with *x*-rays, radium, or radon seeds is in current use. In some cases surgical excision is always more satisfactory being quickly performed without fear of complication and leaving a thin linear scar. These methods are as a rule ineffective in dealing with the deeper subcutaneous and cavernous angiomata and particularly with the advanced type which has acquired an extensive blood supply and now amounts to a cirsoid aneurysm. These methods are not only ineffective but also better avoided, because of the importance of maintaining an unbroken epithelial covering, since loss of viability may lead to sloughing, infection, and haemorrhage with serious risk of grave consequences.

Cavernous.—The useful methods of treating cavernous angiomata are surgical excision, ligation of feeding vessels, injection of sclerosive chemicals, and coagulation by injection of boiling water. In many cases simple surgical excision is effective provided that the angioma is suitably situated, certain types requiring subsequent plastic repair. The size of large angiomata, especially those with deep ramifications, may be reduced by preliminary injections of irritating solutions such as 40 per cent. saline or glucose, ethamolin, or boiling water. Reduction in size from thrombosis follows and surgical excision may then be facilitated. The same reduction in size or even complete thrombosis can sometimes be effected by the implantation of radon seeds.

Ligation of the vessels feeding the angioma is never necessary in the absence of pulsation but is sometimes useful as an adjunct to sclerosis and where surgical

excision is impossible as when both eyelids are involved. It is necessary to remember that the vessels feeding a haemangioma arise from the blood vessels supplying the part concerned, but that the blood passing through the angioma is a circulation by itself and independent of adjacent tissue. When the angioma is arteriovenous in type the shunt of blood may on occasion be so great that the quantity available for nourishing neighbouring tissues is reduced even to the extent of producing ischaemic lesions.

INVOLVEMENT OF NEIGHBOURING TISSUE.—The subject of haemangiomata is a suitable one by which to pass from the more common superficial tumours to the less common deep ones involving the orbital walls or neighbouring tissues. Angiomata of the bony walls of the orbit are uncommon but well known, and occur in capillary and cavernous forms. The typical radiographic appearances of radiating trabeculations give considerable help in making a firm diagnosis.

Although uncommon in themselves, angiomata may be reckoned among the more common causes of exophthalmos by the creation of a space-occupying lesion posterior to the globe. The following types are recognized:

(*a*) Capillary.
(*b*) Cavernous.
(*c*) Angioblastic or hypertrophic.
(*d*) Racemose or cirsoid.

The angioblastic type is firm, being composed of a solid mass of endothelial cells with a minimum of small patent vessels, the lumina becoming obliterated by the proliferation of embryonic epithelium.

The racemose type is composed of a pulsating mass of dilated, thickened, and tortuous vessels. They occur in adults and have a relatively sudden onset. They may represent an ordinary cavernous angioma which has established a communication with a neighbouring artery or arteriole. After this communication has been established the mass becomes locally destructive by reason of constant arterial pulsation. These tumours may erode the walls of the orbit and surrounding structures and even lead to fatal haemorrhage.

A characteristic of haemangiomata, except those of the cirsoid type, is that they do not show unlimited growth but tend to reach a certain size and then remain stationary. This is an important point when considering treatment in a difficult case.

Two noteworthy characteristics of this type of 'tumour' in the orbit are:

(1) The mobility of the eye is unaffected.

(2) The variations in size may result in exophthalmos. These variations may be spontaneous and may be due to simple venous stasis from coughing, crying, bending the head down, or compression of the jugular vein.

Sometimes the haemangiomatous nature of the lesion is revealed by an extension forwards rendering it visible from the exterior in a subconjunctival position, or else by the association of a port-wine stain around the eye. When considering treatment, the position, size, and type of angioma must be taken into account and many of the principles discussed for superficial angiomata applied.

DERMOID and EPIDERMOID TUMOURS.—Dermoid and epidermoid tumours of the orbit are common if the para-orbital type is included, but although well-known, intra-orbital dermoids are not frequent. They are found in many situations—external, intra-orbital, intracranial, and in the diplöe.

FIG. 6 (*a*).—External angular dermoid (front view).

FIG. 6 (*b*).—External angular dermoid (lateral view).

External.—The commonest site is the lateral end of the eyebrow where they are known as external angular dermoids (Fig. 6 *a* and *b*). In this situation they give rise to cysts either tense or soft, which are not attached to the skin but which characteristically form a depression in the underlying skull which may be felt clinically. The depression sometimes amounts to a defect with firm attachment of the epidermoid to the dura (Fig. 7).

Intra-Orbital.—These dermoids occur most commonly in the superior temporal region, causing proptosis and requiring to be distinguished from the less common tumours of the lacrimal gland. In this situation a defect may occur in the bone in the form of either a depression or a foramen which is easily demonstrated in the *x*-ray.

Other Sites.—Intracranial extension sometimes occurs, and some cysts appear to arise in the diploe of the frontal bone extending into both orbit and cranium.

FIG. 7.—Mid-line dermoid at base of nose.

The treatment for both dermoids and epidermoids is the same and where possible consists of excision. In the deeper and larger varieties of intra-orbital cyst this may not be an easy matter because of the involvement of neighbouring structures and cavities demanding transfrontal approach. In others the cyst may first be incised with evacuation of its contents and then its wall may be removed piece-meal.

A few words are required regarding the terms dermoid cyst and epidermoid cyst. Although they are closely related in origin and behaviour and require similar treatment, much has been written of their differentiation. The term epidermoid has replaced the older cholesteatoma or *tumeur perlée*; the differentiation between the two is perhaps academic, since both are derived from embryonic nests originating from the primitive ectodermal layer, the actual differentiation depending upon either the time at which the cell nest

developed or the degree or depth of inclusion of the original dermal layer. It was Renak in 1854 who first suggested that the 'pearly tumour' of Curveillier originated in ectodermal nests, and this hypothesis has been very strongly supported by subsequent observers. The evidence, however, rests entirely on the histological features of the tumour itself and particularly on the details of the capsule.

The ectodermal layer of the head end of the foetus develops into both skin and neural tissue. The cause for differentiation of this one layer is speculative but it has been suggested that what is known as "organizer influence" is excreted by the mesodermal tissue or cells which later become neural tissue. Jefferson believes that the epidermoids found in the brain substance or within the membrane may possibly be due to failure of this influence to compel groups of ectodermal cells towards neural differentiation.

Dermoids vary in size from that of a seed to that of an apple. They are encapsulated and oval, round, or hourglass in shape. They are soft and usually cystic, the actual consistency of the contents being determined by the presence of sebaceous material, fat, and cholesterol crystals in varying proportions. The presence of hair has been regarded as pathognomonic of a dermoid but intermediate forms have been found. Microscopically the wall of a dermoid resembles skin and one can distinguish from without inwards a fibrous capsule, a connective tissue layer containing blood vessels (especially at the site of the dermoid tuft which represents the original site of the dermal implantation), and an inner epithelial layer. This inner layer varies in thickness but resembles skin, there being a number of layers of cells, the innermost being flattened and without nuclei. The wall nearly always shows some evidence of inflammatory irritation.

Epidermoids are simple in nature, and form a more solid mass which may be described as being made up of two layers: the outer layer, or stratum durum as it is called, is formed of layers of collagen fibres with little or no cellular formation; it is this outer layer which gives the epidermoid its characteristic appearance. The inner layer forms the interior with a depth of from two to ten cells; fine granules of keratohyalin are scattered throughout the cytoplasm of these cells and the interior of the cyst is composed of accumulated products of the desquamated epithelial layer. These tumours are of course quite different from the cholesteatomata that occur in the middle ear; the latter are associated with inflammation and consist mainly of epithelial debris, granulation tissue, leucocytes, and cholesterol crystals which are the accumulated products of excess desquamation and reaction to inflammation.

OSTEOMATA.—Tumours arising in the walls of the orbit may be either benign or malignant, primary or secondary, or due to one of a group of miscellaneous diseases of doubtful aetiology.

Osteomata are described as either cancellous or ivory but the latter term is the better. Ivory osteomata occur in almost any part of the skull including

the orbit. They are often dome-shaped and are formed of very hard, mature bone. They are found in both sexes in later life, and are slow-growing and painless. They sometimes follow trauma and after some years of growth tend to come to a standstill. On the vault of the skull they are usually symptomless but when they occur in the orbit proptosis may follow or in advanced cases blindness may result from pressure on the optic nerve. Their usual form is sessile like a limpet and covered with periosteum, the surface being hard and frequently polished. Occasionally, small compact pedunculated tumours are found, which have a short stout pedicle and a mushroom-like head. They are composed throughout of mature, compact bone continuous with the outer table of the adjacent bone and formed of concentrically-arranged laminae containing small haversian systems.

A special type of these osteomata is that which occurs in either the frontal or the ethmoid sinus or in the antrum of Highmore; many remain small and undetected, but others grow steadily larger and sooner or later produce subjective or objective symptoms. They enlarge in a centrifugal manner destroying the bony walls of the sinus by pressure atrophy. In this position symptoms arise of inflammation or obstruction of the sinus. Later they spread into the cranial cavity, nose, and orbit, causing pressure symptoms, proptosis, and sometimes the formation of mucoceles or aeroceles.

The precise aetiology of these tumours is not known. Associated infection is more likely to follow than to cause them. A history of trauma is common but its association is difficult to prove. The ethmoid type is formed in cartilage but those on the frontal bone in membrane. In this latter region however the frontal sinus continues to grow until after puberty and it may be that islands of cartilage are misplaced and stimulated to grow, possibly by trauma. The treatment of these osteomata often involves a complicated neurological operation; in the old days it terminated only too frequently in meningitis and cerebrospinal rhinorrhoea.

The so-called cancellous type of osteoma is usually due to an underlying meningioma and is better known as a hyperostosis (Fig. 8). Amongst the commoner sites are the olfactory groove and the lesser wing of the sphenoid. A meningioma developing in one of these positions, often of the *en plaque* type, invades the underlying bone and causes new bone formation. Hyperostosis of this type is often the cause of exophthalmos, and such a diagnosis may be confirmed by an appearance of fullness in the temporal

FIG. 8.—Hyperostosis of frontal bone due to underlying meningioma.

fossa, or of thickening of the sphenoidal wings, or it may be seen by *x*-ray or may cause an increase of cerebrospinal fluid protein.

Of malignant tumours of the bone around the orbit, osteogenic sarcoma and fibrosarcoma are rare but secondary tumours are more common. A particular example of this is neuroblastoma—the so-called Hutchison's syndrome. Secondary deposits are also rarely found as the result of some haemopoietic disease, such as lymphatic leukaemia in children and myelogenous leukaemia in adults.

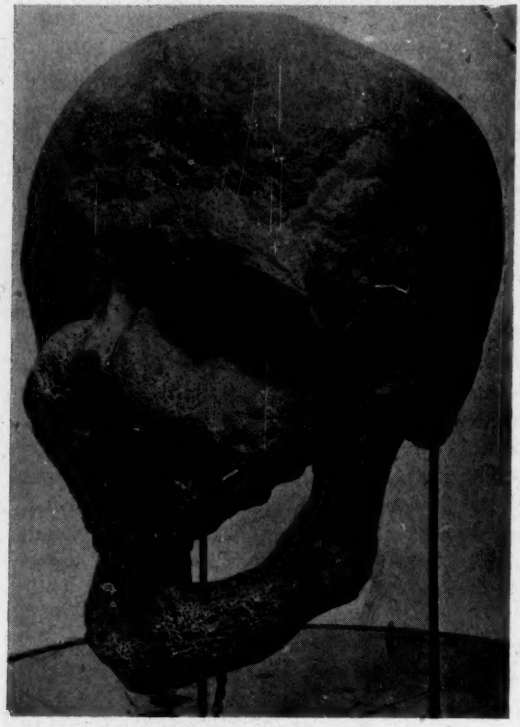

FIG. 9.—Skull of case of leontiasis ossea (Royal College of Surgeons).

In Schüller-Christian disease, alternatively known as xanthomatosis, deposits of lipoid material occur in the membrane, bones, lymphatic glands, and viscera. *X* rays display the typical punched-out appearance of the bone.

Paget's disease attacks elderly people and occasionally picks out one bone such as the upper jaw. A similar deformity may arise from leontiasis ossea (Fig. 9), a condition of bone overgrowth of uncertain origin, which produces asymmetrical deformity with proptosis of one or both eyes and in late cases optic atrophy.

This survey of periorbital tumours, although comprehensive, may have omitted a few rare tumours which should have been included, but I have confined my remarks to clinical material that has come under my care during the past thirty years.

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BINOCULAR WHITE FROM RED AND GREEN, AND THE THREE-COMPONENT THEORY*

BY

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RECENTLY Hurvich and Jameson (1951) have criticized certain experiments designed to show whether yellowness is synthesized from redness and greenness (as the three-component theory of colour vision holds), or is given by the activity of a separate (yellow-blue) receptor in accordance with the opponent-colours (Hering) theory and its derivatives.

These were experiments in which a red stimulus was supplied to one retina and a green one to the other. If the observer obtains a binocular yellow sensation, this could be taken to prove that its yellowness (hence, presumably, monocular yellowness also) is created centrally from the activities of redness receptors and greenness receptors. Hurvich and Jameson did not review the whole history of such haploscopic presentation of red and green stimuli, but singled out the particular experiment of Hecht (1928) with filtered lights, and its repetition with modern narrow-pass filters by Prentice (1948).

Quite properly, these experiments were considered to prove nothing, since in each case the red stimulus employed afforded a slightly *yellowish*-red sensation and the " green " stimulus was really a *yellow*-green one. There being a yellow aspect to the hue of each monocular colour, the presence of yellowness in the binocular experience would be in no way mysterious according to any theory of colour vision. What seemed, however, to call for explanation was the disappearance of the redness and the greenness—if these were *not* being integrated into yellowness.

Hurvich and Jameson speak of this disappearance as the result of a " central cancellation ", the mechanism of which, they consider, " constitutes a real problem ". The problem is real only if the redness and greenness do in fact disappear without having been used up in making yellowness. One may suspect that in the Hecht experiment there is not nearly enough total yellowness in the monocular sensations to account for the magnitude of the binocular yellowness; but to test this suspicion quantitatively would be very difficult to say the least. Easy and genuine proof of mutual cancellation of redness and greenness, as against their synthesis into yellowness, would however come from a situation in which red and green sensations, neither of which had any other hue-aspects, disappeared upon combination without the emergence of any yellowness whatever.

Hurvich and Jameson perceived this, and claim to have performed the crucial experiment. For each of the two observers (LMH, DAJ) a mixture of $\lambda 671$ mμ and $\lambda 440$ mμ was devised which afforded a " pure " red sensation,

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and a third monochromatic light was chosen which gave a " pure " green sensation—λ498.1 mμ for DAJ, λ489.4 mμ for LMH. The authors used " pure " not in the colorimetric sense, nor (as is common) to describe the hue of any monochromatic light, nor to describe a stimulus yielding a fully saturated sensation, but to describe a colour-experience having in it only a single kind of huedness (redness, or greenness) together with the inescapable desaturative " whiteness ". Their usage will be employed here to avoid confusion (although " unique " and " unitary " are established terms having the same significance).

When LMH and DAJ each viewed haploscopically the stimuli which satisfied them respectively as pure green and pure red, their binocular experience was either a reddish or greenish colour depending upon intensity-ratios; but it was never a yellow, and at one intensity-ratio it was " a neutral, hueless sensation ", *i.e.*, what is generally called *white*. They considered this result to be " in direct conflict with the ordinary assumptions of a three-component theory " although it is "predicted by traditional four-component theories, where red and green are assumed to be opponent or complementary colours ". They admitted, however, that possible modifications of the three-component theory would " enable it to account for the emergence of a white sensation from a mixture of pure red and pure green ". This is ambiguous, as it is not clear whether they are challenging the three-component theory to explain the result of a mixture of stimuli or that of a " mixture " of *sensations*. Haploscopic stimuli cannot be said to be undergoing " mixture " and to speak of whiteness as arising from a mixture of red*ness* and green*ness* begs the question. It has first to be demonstrated that whiteness is ever " mixed " (synthesized) from huednesses of whatever number and kinds.

Hurvich and Jameson are emphatic in refraining from a choice between theories on the basis of their one surprising experiment. But others will make the choice, and the signs are already evident (New York Times, 1951). The authors themselves speak of a " mysterious, synthetic central emergence of the quality yellow "—which is the mode of expression of a critic, not an adherent, of the three-component theory.*

Let the validity of Hurvich and Jameson's crucial experiment be temporarily assumed. It appears to demonstrate that when monoccular sensations contain no hues but red and green the binocular sensation contains no yellowness because redness and greenness cannot synthesize yellowness, and also contains neither redness nor greenness because these have " cancelled " each other as if they were perfectly opponent qualities such as Hering contemplated. Haploscopic yellowness and blueness can also disappear with the emergence of only whiteness binocularly, as is well known; but, since yellow and blue are " complementary " under the three-component theory as well as being " opponents " under the six-component

* It seems strange that psychologists, of all people, should call the synthesis of one sensory quality from two others " mysterious ", as if it were incredible and probably non-existent. They were psychologists (Alrutz, Bentley) who demonstrated long ago that dermal wetness is synthesized from coldness and pressure, and that burning hotness is synthesized from coldness and mild warmth.

theory, Hurvich and Jameson did not even mention Hecht's execution of this latter experiment, let alone repeat it using " pure " stimuli.

Would, now, a binocular sensation of whiteness from haploscopic red and green stimuli " shake the three-colour theory " and " support the four-component colour theory " ? Not at all. It needs to be remembered that any and every colour-vision theory so far proposed is purely *ad hoc* in that it is tailored to the facts of monocular colour vision. If binocular facts are found which appear to conflict with a given theory, they cannot be deemed to destroy it. If binocular facts are found which appear not to conflict with a particular theory, they cannot properly be considered to support it. The peculiarly binocular portions of the human visual apparatus are secondary impositions upon the monocular systems. For two reasons, they cannot legitimately be expected to possess, *necessarily*, counterparts of all monocular capacities; they are phylogenetically newer, and serve to supplement rather than to duplicate the potentialities of monocular vision; and, since haploscopic presentation of chromatically different stimuli does not occur in the natural environment of prescopic vertebrates, the essentially binocular apparatus need never have evolved any machinery for dealing with it.

This argument is not at all strong *if* whiteness is centrally synthetic, and *if* central binocular sensory " fusions " do take place in respect of visual attributes other than chromaticness. Several years ago, however, I concluded against the existence of genuine binocular physiological fusion of anything *but* chromaticness (Walls, 1948), and, at about that time, I began to teach a version of the three-component theory which denies the synthetic character of whiteness.

Newton is seldom if ever given proper credit for having understood that colour is subjective and not a physical property of lights and pigments. Despite this understanding, no sooner had he produced the prismatic spectrum than he committed the flagrant stimulus error that was later taken into the three-component hypothesis of Thomas Young.* Since a white *light* can be made by mixing coloured *lights*, almost everyone from Newton on down has supposed that a white sensation is mixed from coloured sensations. Seldom has any three-componentist spoken against this; but Southall (1924) did say that white may be the most fundamental and " elementary " of all visual sensations, and that he saw no reason to infer that the sensation of white is complex—composed, for example, of a sensation of yellow plus a sensation of blue.

In three-component thought, separate redness, greenness, and blueness receptors are conceived to arouse respective pro-sensational processes, which are blended to produce the experienced sensation. The traditional view holds that if a pro-sensation could stand alone the individual would experience a colour having a pure hue and some unimaginable degree of saturation. Pure yellowness results from the mergence of magnitudes of

* Historically, this was not the first but no better than the second (perhaps even the third) theory to explain colours as being comprised from three sensory components. In the much earlier three-component theory of Palmer (1777), whiteness was explained as due to the absence of a basis for huedness.

redness and greenness which are, in some sense, " equal ". Whiteness is also synthetic, but requires all three pro-sensations to be aroused and to be " equal ".

If whiteness were synthesized from three pro-sensational components, then in photopic adaptation, with his rods greatly desensitized, a protanope could not experience whiteness from a piece of white paper or from monochromatic light at the wave-length of his neutral point. Lacking the redness pro-sensation, he would see such stimuli as highly saturated blue-greens. A tetartanope, who lacks blueness receptors, would perceive whites and his two neutral-point wave-lengths as strong yellows. A congenital atypical achromate who was simultaneously protanopic and tetartanopic would see everything in rich green.

These people do *not* see white stimuli as coloured, but as white in the normal's sense of the word. This is more than merely to say, as the cautious do, that, *e.g.*, a protanope calls his neutral-point light white only because it looks the same to him as a white light does, with both stimuli giving him a sensation of unknown and unknowable quality. These loss-dichromates and achromates, be it noted, have their perfectly normal scotopic (rod) whiteness to tell them what " white " means to the normal. If a white paper looked any different, qualitatively, to a colour-blind in photopia from what it did in scotopia, he would be able to say so. Very obviously, it does not.

This is the foremost of the reasons why I append, to the three-component explanation of huedness, *the excess hypothesis* (of saturation). The excess hypothesis explains whiteness quite otherwise than by synthesis, makes the three-component theory workable, and makes a *six-component theory unnecessary.* It is the " further modification "—capable of explaining a binocular genesis of whiteness from haploscopic red and green stimuli (if this does indeed occur)—which Hurvich and Jameson have asked for. Further evidence for it, and for the three-component theory proper, is being given elsewhere (Walls and Mathews, 1952). According to the excess hypothesis:

(*a*) A pro-sensation which exceeds a finite magnitude of another pro-sensation introduces its specific huedness into the sensation.

(*b*) If two pro-sensations exceed a third, the huednesses of both appear in the sensation (excepting where yellowness is formed, accompanying an excess of redness or an excess of greenness, or standing alone).

(*c*) A pro-sensation which exceeds no other introduces only desaturative whiteness into the sensation, whether it stands alone, or is exceeded by one other pro-sensation, or by two.

In this view whiteness exists not by synthesis, but by default of any basis (in an imbalance of pro-sensations*) for huedness. Yellowness however, in its synthetic origin, remains a " special case ".

* Willmer (1949) came close to a formulation of the excess hypothesis when, from his studies of central-foveal vision in certain rare deuteranopes, he was led to say: " Presumably, colour sensations must derive from differences in response between two or more pathways, and not as the result of the response along a single pathway when this cannot be compared with the response along another or other pathway "

Returning now to the situation where whiteness has been claimed to result from haploscopic stimulation with pure red and green lights. What is the sensory situation *via* each eye singly? A "pure" sensation is being given because one pro-sensation is in excess and the other two are equal and hence find expression only as whiteness. In monocular vision, redness and greenness standing thus alone over whiteness, if equal to each other, would synthesize pure yellowness under the three-component theory. In haploscopic vision, however, equal redness and greenness pro-sensations need not necessarily synthesize anything at all under the excess hypothesis. They will each come into the sensation as whiteness—not through synthesis of the latter, nor because they "cancel", but simply because they are equal—*if* the peculiarly binocular sub-perceptual apparatus has no provision for synthesizing yellowness from them. I have already asked, "why should it?"; and I have already said that I can see no reason why any theory of the monocular colour-vision mechanism should be expected to stand ready to account for anything and everything that may be found to happen, or not to happen, in binocular vision. Pure redness and greenness could well behave like "complementaries" in normal binocular vision just as they do in the monocular vision of a tetartanope. For that matter, so could redness and blueness, or blueness and greenness.

The synthetic origin of monocular yellowness has been demonstrated in no less than three independent researches, where means were found of activating the redness and greenness receptors separately with monochromatic "pure" yellow light (Göthlin, 1943; Otero, Plaza, and Casero, 1948; Stiles, 1949). No bolstering hypothesis is necessary to explain such dissectibility of yellowness, for a prediction of this is tacit in the traditional three-component theory. Not tacit, however, is a consideration which has always seemed embarrassing, but becomes less so in the light of the excess hypothesis (and the complete desaturation of binocular red-plus-green, if this be a fact).

This is the extremely low saturation of even monochromatic yellow. It is generally taught that the blueness receptors have no responsivity whatever at wave-lengths as long as that of the locus of pure yellow. Yet, yellow is by far the least saturated colour in the spectrum. It is as if when redness and greenness do synthesize—even in monocular vision—as much or more whiteness is "formed" (without need of any blueness), as yellowness. This has led to at least three independent postulations that one pro-sensation may desaturate another (Hamilton and Freeman, 1932; Hecht, 1931, 1934; Rawdon-Smith, 1938)—at any rate, where redness and greenness happen to be the two pro-sensations concerned. Yellowness is perhaps then a special case not only because it is qualitatively unlike its two components but because some of it may be generated when only two pro-sensations are present and equal, where the excess hypothesis calls for only whiteness to result. If there is no blueness activity at the yellow locus of the spectrum,

which is not proved (Walls and Mathews, 1952), then monocular yellowness from redness and greenness is much more of a puzzle than is binocular whiteness from haploscopic redness and greenness.

But, *did* Hurvich and Jameson obtain binocular whiteness from pure redness and pure greenness? It is hard to see how they possibly could have, when one considers what their stimuli were. Each of the two observers—in the particular state of adaptation upon which they standardized—obtained what was deemed pure red from a mixture of $\lambda 671 m\mu$ and $\lambda 440\ m\mu$. DAJ chose $\lambda 498.1\ m\mu$ as providing a pure green sensation, while for this LMH required $\lambda\ 489.4\ m\mu$.

When the red stimulus was viewed with one eye and the green one with the other, each observer experienced a " neutral, hueless " sensation. If this is to be considered to prove or disprove anything, it would have to be true that if the very same stimuli at the very same intensities had been mixed on *one* retina, a hued—and specifically, a *yellow*—sensation would have resulted. Now the stimuli which afforded binocular " neutral " sensations were:

For DAJ: 12.8 mL 671 + 2.5 mL 440 and 0.55 mL 498.1
For LMH: 12.8 mL 671 + 3.0 mL 440 and 0.36 mL 489.4

The first thing that strikes one as strange here is the enormous photometric discrepancy between the left- and right-eyed stimuli. Complementation in monocular vision always requires a greater intensity of the less-saturated stimulus, and the rules of haploscopic complementation are not supposed to be markedly different in this regard.

The next thing to consider is what chromaticity would have resulted if the red and green stimuli of each observer had been mixed without alteration and presented to one retina. DAJ's monocular stimulus would then have been one which, on the International Commission on Illumination (Commission Internationale d'Eclairage) chromaticity diagram, plots at $x = 0.61598$, $y = 0.23502$. This is no yellow, but a purple having a dominant wave-length of 494.1 $cm\mu$ and an excitation purity of 89.8 per cent., with reference to a generally-accepted standard white (C.I.E. Illuminant C). LMH's monocular stimulus would plot at $x = 0.61147$, $y = 0.22056$, which is again a purple, with a dominant wave-length of 494.8 $cm\mu$ and a purity of 94.9 per cent. If two moieties of a monocular *purple* stimulus, presented haploscopically, fail to arouse a yellow sensation, this should not surprise anyone.

In correspondence with Dr. Hurvich, I raised the question of what the monocular visual result of their combination of stimuli would have been. It appears that Hurvich and Jameson did view the combined stimuli monocularly, but in their paper " omitted any reference to the monocular results so as not to be sidetracked . . . from (their) major point " Hurvich (1951). The monocular result was, however, most revealing; for: " with regard to the question of the difference between monocular and binocular mixture results, qualitatively they are identical " (*Ibid.*).

This means that Hurvich and Jameson obtained their binocular whiteness-

sensation from stimuli which, in monocular vision, were *complementary* since in a particular (the same ?) intensity-ratio they afforded a white sensation there also. They could not have been made to give a *yellow* sensation monocularly. The fact that they did not do so binocularly ceases to have anything to do with the relative merits of the three-component theory and other theories of colour vision.

No-one has ever found pure red and pure green photopic stimuli to be complementary, or to give anything but yellow-green, yellow, or orange in near-equal intensity ratios. But then, no-one has ever found the " pure " stimuli to be located in the spectrum where Hurvich and Jameson found theirs. For example, their respective pure greens were $\lambda 489.4\ m\mu$ and $\lambda 498.1\ m\mu$. These values " straddle " Hering's *Urgrün* stimulus—$\lambda 495.0\ m\mu$—which is generally regarded not as a green but as a " pure " blue-green, and was chosen by Hering to be a perfect complement of his *Urrot* stimulus (as demanded by his own theory). Hurvich and Jameson tabulate the " pure green " wave-lengths they were able to find in 50 years' literature, but without noting that the mean value for the subjects tabulated is $\lambda 512.1\ m\mu$, quite distant from their own two individual values.

LMH found pure yellow at $\lambda 588.9\ m\mu$ whereas for DAJ it lay at $\lambda 579.5\ m\mu$. To account for a displacement of pure yellow to a wave-length even as long as $584\ m\mu$, Judd had to postulate an abnormally heavy macular pigmentation and an abnormally reddish colour of the macular pigment, when he assisted Sloan and Wollach (1948) to interpret their subject " D. D. ", who had one deuteranopic eye and one mildly deuteranomalous eye (Walls and Mathews, 1952). The expected spectral locations of pure yellow and pure blue are at $\lambda 575\ m\mu$ and $\lambda 470\ m\mu$ (Judd, 1948). Even $\lambda 584\ m\mu$ is a reddish yellow in normal colour vision (Sloan and Wollach, 1948), and the sodium lines are generally called orangeish by expert colourists—$\lambda 600\ m\mu$ being central orange.

The differences between DAJ and LMH are such that it looks unlikely that they can *both* have normal colour vision. LMH's pure-hue locations are reminiscent of those for the slightly anomalous " normal " eyes of two unilateral deuteranopes and one unilateral extreme deuteranomal in the literature (Sloan and Wollach, 1948; von Hippel, 1880; Reichert, 1916; Walls and Mathews, 1952). Hurvich (1951) states, however, that LMH exhibits no degree of deuteranomaly on standard colour-vision tests.

The differences between the two observers thus remain unexplained. The differences they show in common, from reasonable expectations, also demand explanation. Each obtained a white sensation, binocularly and monocularly, from stimuli which " should " have appeared coloured (though with the hue of purple, not yellow in any case). One can only suppose that their state of adaptation accounted for this, and perhaps accounts for the spectral locations at which they found their pure hues.

Hurvich and Jameson (1951) describe their preparation for viewing any

of their stimuli as a 10-minute stay in darkness which, they consider, put them in " a neutral state of adaptation ". Ten minutes is long enough to produce complete dark-adaptation of the cones of the average individual. Following such preparation, Hurvich and Jameson proceeded to view stimuli at photopic levels, as intense as 15.8 millilamberts. It is easy to imagine that the huedness of the sensation in their crucial experiment was simply " glared out " by their excessive sensitivity, making the sensation an acceptable " white ".*

It should be clear that Hurvich and Jameson's must not be allowed to be the last repetition of the Hecht experiment. Their basic idea of viewing haploscopic " pure " red and green stimuli was splendid. Such stimuli should however be devised for an indisputably colour-normal observer under the photopic conditions which are optimal for colour vision. His preliminary adaptation should be to an extensive Munsell N 5/ surface illuminated with a true physiological white light (probably 7500° K ; Walls and Mathews, 1952), at the luminance level of the chromatic stimuli which he is later to view. Each of the chromatic stimuli should be presented in a bipartite field containing a standard white also.

On the basis of such a pursuit of Hurvich and Jameson's excellent idea, it should at last be determinable whether dextro-ocular redness and sinistro-ocular greenness, each standing alone in its eye's sensation except for desaturative whiteness, synthesize binocular yellowness or disappear. If they disappear, it will be time enough to spend more words in wondering why.

*LMH and DAJ had only a memory-standard of " neutrality " in their experiment. How dangerous this is, is seen whenever a dichromate is allowed to determine his neutral-point wave-length on a monochromator—first without, and then with, a white comparison field (Walls and Mathews, 1952).

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INFLUENCE OF TERRAMYCIN ON THE COURSE OF EXPERIMENTAL OCULAR TUBERCULOSIS*

COMPARATIVE ACTIVITY OF TERRAMYCIN, STREPTOMYCIN, AND BOTH ANTIBIOTICS COMBINED

BY

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ALTHOUGH the broad antimicrobial spectrum of terramycin, the antibiotic recently isolated (Finlay and others, 1950), has now been sufficiently delimited, its influence in tubercular infections has not been established with any certainty.

Preliminary research has shown that the *Mycobacterium tuberculosis* has, *in vitro*, a certain degree of resistance to the action of the antibiotic. This notwithstanding, the earliest experimental research on tuberculous infection in animals (guinea-pigs and mice) has shown that the drug has a therapeutic effect (Steenken and Wolinsky, 1949), although it was possible to use only very small doses in the guinea-pig because of the toxic reaction produced by terramycin in this animal.

The report of Hobby and others (1950) on the therapeutic effect exerted by terramycin on experimental infections in mice seems to indicate that a dose of 7.1 mg. terramycin per day, administered subcutaneously to mice, is sufficient to produce an inhibiting effect on experimental tuberculosis.

As it seemed desirable to continue researches into the influence of this antibiotic in tubercular infection, we accepted the invitation of the Pfizer Company to investigate its action in experimental ocular tuberculosis.

We had to choose whether it would be better to induce the infection in normal animals or in animals allergized by a previous bacterial infection in another part of the organism. Although this second method causes the ocular tubercular infection to follow a more gradual course, and does, in fact, approximate more closely to the course of the clinical ocular infection, it does not lend itself so well to an evaluation of the effectiveness of an anti-tubercular drug because of the basic influence exerted by the reaction of the organism. Therefore we decided to conduct the experiment on normal, non-allergized animals (rabbits).

Technique

Into thirty male rabbits having an average weight of 1.8 kg. we introduced, into the anterior chamber, 0.1 ml. of a suspension of Koch's bacilli (human variety), obtained by diluting in normal saline physiological solution a tuberculous patina

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from Petragnani's culture medium, in the proportion of 1 mg./ml. Into the eyes of the animals thus infected we then instilled for three consecutive days a drop of atropine; all signs of ocular traumatic irritation generally disappeared by the second day.

Starting on the fourth day (that is, exactly 72 hrs after the infection), the animals were divided into four groups:

I. Controls: no treatment—six animals.
II. Treated with streptomycin—eight animals.
III. Treated with terramycin—eight animals.
IV. Treated with streptomycin and terramycin combined—eight animals.

Route of Administration and Dosage.—Streptomycin was administered by the parenteral route in daily doses of 100 mg. (two 50-mg. intramuscular injections at 8 a.m. and 8 p.m.)*.

Terramycin was administered intramuscularly for ten consecutive days, in doses of 100 mg. per day per animal. The terramycin powder (hydrochloride) was dissolved in water and the solution adjusted to a *p*H of 6.5 to 7 by the addition of sodium chloride and sodium borate. The drug was given in three daily doses, administered at 9 a.m. (25 mg.), 4 p.m. (25 mg.), and 11 p.m. (50 mg.).†

We noted that the parenteral introduction of terramycin causes in the animals a certain degree of motor excitation, which disappears rapidly, and at the point of injection we saw a certain degree of necrosis. This fact, together with the loss of weight and lack of appetite observed in the animals after the first few days of treatment, induced us, after 10 days of uninterrupted parenteral therapy, to continue the administration of terramycin by the oral route, in the same 100-mg. doses per day per animal. In order to promote as constant as possible an assimilation of the drug, the solution of terramycin was mixed with some solid food (bread). This promptly caused the animals to resume their normal weight. Such oral treatment was continued without interruption for 20 days, thus bringing the total period of treatment with the antibiotic to 30 days. On that date all treatment was discontinued.

Course of Infection

I. Control Animals.—Taking an average of the times at which the various tubercular manifestations appeared in the individual animals of this group, we observed the first signs of specific phlogosis (conjunctival hyperaemia and iritic hyperaemia) about the 12th to 13th day of the infection. The appearance of the nodules on the iris, as we could observe under the biomicroscope, occurred about the 16th to 17th day, and was followed by the establishment of marked congestion and oedema of the iris during the period from the 18th to the 24th day. Between the 20th and 22nd days, the cornea began to be invaded by pannus, which, starting from the upper sector, subsequently extended to almost the entire membrane. The eyeball appeared in incipient buphthalmos during the fourth week, and, during the fifth week, a process of panophthalmitis set in, leading in four animals out of six to the perforation of the bulbus between the 45th and

* We preferred to administer the streptomycin in two daily doses rather than in a single dose, to obtain a concentration in the blood as constant as possible.

† Although a sufficiently constant level of terramycin in the blood can also be obtained by means of a single daily administration, we here also favoured a divided dosage, to ensure the most constant levels possible.

52nd days of the infection. This was followed by the regressive phenomena, finally resulting in atrophy of the eyeball. In the two animals, in which such perforation did not occur, the outcome was likewise total atrophy of the bulbus.

II. Animals treated with Streptomycin.—Confirming previous experience, the infection assumed a rather favourable course. Although the first signs of inflammation of the iritic membrane appeared somewhat later than in the control animals (on the 14th to 15th day), the intensity of the iridic congestion and oedema and the number and diffusion of the tuberculous nodules were found to be markedly reduced. The corneal pannus did not appear in all the animals, and, where it did appear, was limited to the periphery of the membrane. In none of the animals did the phlogistic process reach the stage of tuberculous panophthalmitis, and the outcome consisted of atrophy of the iris, more or less marked posterior synechia, and, now and then, partial pupillary occlusion. The bulbus never appeared in a state of buphthalmos. Once the infection had ceased, the animals visibly retained a certain degree of visual acuity. All signs of phlogosis disappeared on the 50th day after the infection.

III. Animals treated with Terramycin.—The initial course was decidedly more favourable than in the untreated control animals; the first signs of inflammation generally appeared after the 15th day of infection, and these were attenuated and limited. There was also a reduction in the number and size of the specific nodules appearing on the iris. The subsequent course reflected a certain attenuation, and, above all, a delayed development, which was clearly visible up to the 25th to 28th day of the infection. On the other hand, after this date, we noted a definite aggravation of the specific symptoms which, when the treatment was suspended (on the 30th day), had become nearly as intense as those in the control animals. The final outcome was perforation and atrophy of the bulbus in half the cases, and atrophy without passing through the stage of perforation in the remainder. It should be noted that a similar result was seen later in the control animals, so that the phlogosis, although more attenuated on the whole, was of longer duration.

IV. Animals treated with Terramycin and Streptomycin combined.—On the whole, the course of the infection was similar to that observed in the animals treated with streptomycin only.

It is, however, worthy of note that the first signs of phlogosis appeared much later (after the 20th day in all the animals). The subsequent course and the ultimate inflammation were similar to those in the second group. The tuberculous nodules were scarce, the congestion and oedema of the iris limited, and the pannus on the cornea confined to the upper sector of the membrane. The final outcome was corneal nubeculae, partial atrophy of the iris, posterior synechia, and, at times, an occluded pupil. All signs of inflammation disappeared on the 50th to 55th day in all the animals.

Discussion

A comparison of the action of terramycin in experimental ocular tuberculosis with that exerted by streptomycin under the same conditions and in identical doses shows that the latter has a more favourable influence upon the course of the infection. However, it seems to us that terramycin also

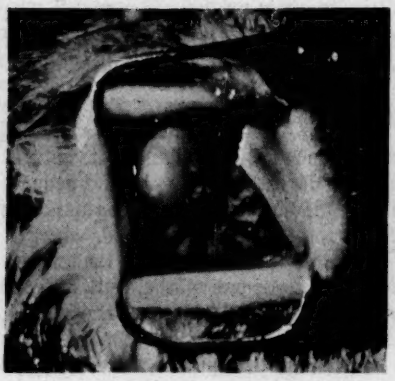

FIG. 1.—Untreated control eye (20th day from infection). Beginning of corneal pannus; congestion and oedema of iris; tuberculous nodules on surface of iris (Rabbit No. 5).

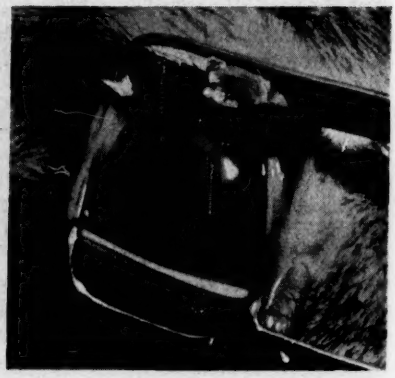

FIG. 2.—Streptomycin-treated eye (20th day from infection, 17th day from start of treatment). No pannus; slight congestion and oedema of iris; small tuberculous nodules on surface of iris (Rabbit No. 11).

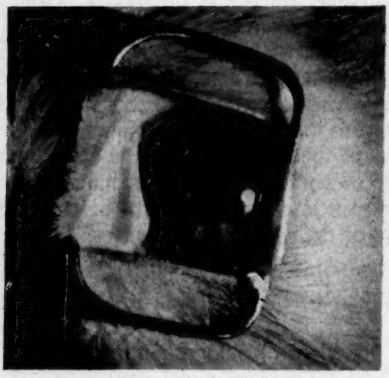

FIG. 3.—Terramycin-treated eye (20th day from infection, 17th day from start of treatment). Similar appearance to Fig. 2 (Rabbit No. 16).

FIG. 4.—Streptomycin/terramycin-treated eye (20th day from infection, 17th day from start of treatment). Only slight congestion of iris nodules not yet visible on surface of iris (Rabbit No. 26).

has a certain measure of effectiveness against tuberculosis, as evidenced by the delayed appearance of tuberculous manifestations in the iris and of the other classic symptoms of inflammation. On the other hand, we were able to observe that the delaying effect on tuberculosis is considerably reduced after the 20th or 25th day of treatment, as if the bacteria had acquired a certain degree of immunity to the antibiotic, and that it ceases completely after the suspension of the treatment, whereas the effect continues without any flare-up in animals treated with streptomycin.

FIG. 5.—Untreated control eye (28th day from infection). Cloudiness of cornea and evident corneal pannus; buphthalmos; appearance of iris not visible; incipient panophthalmitis (Rabbit No. 3).

FIG. 6.—Streptomycin-treated eye (28th day from infection, 25th day from start of treatment). Transparent cornea; congestion and oedema of iris; tuberculous nodules visible on surface of iris (Rabbit No. 13).

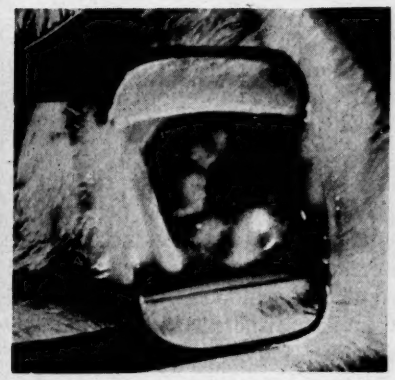

FIG. 7.—Terramycin-treated eye (28th day from infection, 25th day from start of treatment). Beginning of corneal pannus; marked congestion and oedema of iris; large tuberculous nodules clearly visible (Rabbit No. 19).

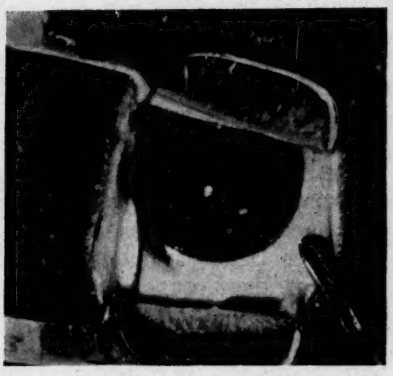

FIG. 8.—Streptomycin/terramycin-treated eye (28th day from infection, 25th day from start of treatment). Transparent cornea; slight congestion and oedema of iris; small tuberculous nodules visible on surface of iris (Rabbit No. 27).

The combined terramycin-streptomycin treatment resulted in the first signs of tubercular phlogosis appearing after a still longer interval, but the final evolution was no better than in animals treated with streptomycin only.

Thus we can definitely affirm that terramycin has some measure of antitubercular activity, which could be detected even in the severe experimental infection provoked in our experiments.

We feel that it would be useful to compare the activity of terramycin with

that of aureomycin. Woods and others (1950) could not demonstrate that aureomycin had any inhibiting action on the development of ocular tuberculosis in experimental infections provoked in normal rabbits by injections of a suspension of *myco. tuberculosis* (human variety) into the anterior chamber. But there was a substantial difference between their experimental conditions and our own, since in their experiments treatment was instituted on the 12th day, when the first modifications had already occurred, and the doses were smaller (20 mg. per kg.).

These different results from treatment with aureomycin and terramycin agree with the observations of Steenken and Wolinsky (1949) in general tuberculosis of the guinea-pig, and confirm that aureomycin and terramycin behave differently in tuberculous infections.

We must conclude that, contrary to what has been found regarding most of the characteristics of terramycin and aureomycin (antibacterial spectrum, and effects on micro-organisms, both Gram-positive and Gram-negative, as well as absorption, excretion, etc.), which are almost identical, a different action exists with respect to tuberculous infections. Here terramycin—at least under the conditions of our investigation—displays a definite degree of activity, though this is slight compared with that of streptomycin.

Summary

The influence of terramycin on the course of experimental ocular tuberculosis induced by injections of Koch's bacilli into the anterior chamber has been investigated, and comparison made with the activity of streptomycin under the same experimental conditions and in the same dosages.

The action of terramycin was found to be decidedly inferior to that of streptomycin, but there was definite evidence that terramycin delayed the appearance of the first signs of tuberculous phlogosis and the succession of the other classic symptoms of inflammation. After the suspension of treatment there was a prompt recurrence of phlogosis, and the final outcome was the same as in the control animals, whereas in those animals where streptomycin was used, the inhibiting activity continued. When both antibiotics were used in combination, a very slight advantage was observed over the effect of streptomycin used alone.

A comparison of the results obtained by the authors with those obtained in a previous investigation by Woods and others (1950), in which aureomycin was used, although under different experimental conditions, reveals that, whereas aureomycin is incapable of inhibiting the course of experimental tuberculous infections, terramycin—at least under the experimental conditions observed by the authors—has a slight but definite inhibitory activity.

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OCULAR ONCHOCERCIASIS*

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ONCHOCERCIASIS is caused by infection with the adult filarial worm *Onchocerca volvulus*; the microfilariae of this worm develop in the body of man and sometimes penetrate the tissues of the eye where they set up pathological changes leading to blindness; embryos may also be found in the skin, in lymph glands, in the fluid of hydroceles, and in effusions into joints. The disease has been reported from central America, and from scattered areas in equatorial Africa in a vast belt of territory which extends from latitude 15° N. to 20° S. (Hughes, 1949); in W. Africa the distribution closely follows that of the fast flowing rivers and streams in which the vector, *Simulium damnosum*, breeds. This association with rivers is known to many Africans. The Moshi tribe of the French Upper Volta have a saying recently translated by Puyelo and Holstein (1950):

La proximité des grandes rivières ronge les yeux.

Hughes noted that Gold Coast fishermen have long blamed the foam on the rapids of the River Volta for their high incidence of blindness.

The incidence of eye complications, based largely on figures for incidence of blindness, appears to vary considerably in different areas: in a recent survey of some 88,000 inhabitants of the French Upper Volta district, Puyelo and Holstein reported blindness rates up to 35 per cent. in one village; Hissette (1932) found 15 per cent. blind in a village in the Belgian Congo; Waddy (1949) reported 10 per cent. in villages in the Northern Territories of the Gold Coast; Strong (1934) found that 5 per cent. among his Guatemala cases of onchocerciasis had " eye disturbances ". At the other end of the scale, Blacklock (1926) in Sierra Leone and Sharp (1927) in the Cameroons found no associated blindness with onchocerciasis.

The total extent of the sociological problem of onchocerciasis cannot at present be assessed, but there is no doubt that it is considerable; the incapacitating effect of the eye lesions, which can be inferred from the published blindness rates in some districts, is tragic, and the general lesions in the skin and other organs cause serious distress to the inhabitants of highly infected areas. Ridley (1950) has pointed out that the possibility that ocular onchocerciasis is the cause of obscure ophthalmic conditions in

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persons who have spent some time in equatorial America or Africa, must be borne in mind by ophthalmologists in other countries.

The bibliography on onchocerciasis has now reached considerable proportions, one published by the Pan-American Sanitary Bureau (1950) giving abstracts of over a thousand contributions to the literature. Few of these dealt with the ocular manifestations and even fewer appeared in English journals. Since the original description by Robles (1919) and Pancheco Luna (1919) from Central America, the eye lesions in established cases have been fully described by Hissette from the Belgian Congo, and by Ridley (1945) from the Gold Coast. These manifestations consist of a vascular conjunctival injection, interstitial nummular opacities of the cornea which may be so extensive as to become confluent, anterior uveitis, choroido-retinal degeneration, complicated cataract, secondary glaucoma, and optic atrophy. In the skin the typical lesion is a dry wrinkling which gives the appearance of premature age, to which Hughes applied the term " presbydermia ". Subcutaneous nodules, consisting of numbers of encysted adult worms, are often found over such bony prominences as the ribs, iliac crests, sacrum, knees, and skull. In severe cases with gross pruritus, lichenification may occur and papular eruptions follow secondary infection. The occurrence of elephantiasis in cases of onchocerciasis has been noted by many writers though a causal relationship has yet to be demonstrated.

The present study is concerned mainly with early cases seen in the Gold Coast, and is an attempt to assess the importance and the diagnostic value of the early ocular manifestations. The necessity for complete ophthalmic examination and investigation in all cases is emphasized in the light of the paucity of signs seen in the eyes of such cases. Tables are given where necessary to support findings, and some cases are reported in full to illustrate specific points. The effects of treatment with Hetrazan and Antrypol are described with special reference to the ophthalmic manifestations; the surgical treatment of two cases complicated by secondary glaucoma is discussed, and comments are made upon the results of administration of riboflavine in a limited number of cases which showed early visual defects. All the cases were examined by the writer, and any pathological examinations were done personally or by Dr. M. H. Hughes of the Medical Research Institute in Accra. The principal difficulties, already mentioned by Ridley, arose from the illiteracy and low intellectual standards of the majority of sufferers; these often make it impossible to obtain accurate estimates of visual acuity and fields by subjective methods, and also cause many patients to postpone seeking medical advice until the disease is fairly advanced. In the hope of overcoming these difficulties, surveys were done on 270 industrial labourers and 224 schoolchildren in the Lower Volta district, shown by Hughes and Daly (1951) to be highly endemic for onchocerciasis. These surveys, did produce a number of early cases for investigation and treatment. Also a group of literates was collected, who were sufficiently intelligent to

give accurate visual acuities, though not unfortunately visual fields. For the rest, 31 cases which presented at the out-patient department in Accra are cited; these were usually advanced cases with established eye lesions.

Methods of Examination

In all cases the following routine of investigation was adopted. In the first place a general examination was made of the skin, and regions of bony prominences, such as the skull, ribs, pelvic girdle, and knees, were searched for nodules. The general findings in respect of these examinations during the course of surveys are reported elsewhere by Hughes and Sarkies (1951). It was noted then that the severity of most of the manifestations of onchocerciasis increased in direct proportion to the duration of exposure.

With regard to the ophthalmic examination, it was found possible to make accurate estimates of visual acuity only in those subjects who were literate or with whom some common language could be found. The use of such types as Landolt's " C " and the illiterate " E " gave such misleading results in a large number of patients in the lower intelligence levels, that only a rough classification of vision into three categories (blind, some visual loss, and normal) was undertaken. After a general examination using a condensing lens, the eye was investigated under a mydriatic. Both eyes were then examined with an electric ophthalmoscope, starting with a +20 D lens and racking down through the media to the fundus; in nearly all cases a further examination was made with a slit lamp and corneal microscope.

PATHOLOGICAL INVESTIGATIONS.—Various confirmatory investigations have been used in diagnosing onchocerciasis. The method principally employed in the hospital cases of this series was a combination of skin snips and skin smears modified from the techniques of Corson (1922) and Sharp (1926). A slip of skin was lifted with stitch forceps and the epidermis sliced off with a scalpel; this produced a piece of skin about 2 mm. in diameter which was immediately mounted in saline and examined under the low power of a microscope for living microfilariae. One disadvantage of this procedure is that it is not possible to make stained preparations, without which differentiation of the *mf. volvulus* from others, such as *mf. streptocerca* and *mf. perstans*, is not certain. When a stained preparation was required, it was found convenient to make a thick film of the sero-sanguineous exudate from the raw surface of corium left by the skin snip, this was dried and subsequently stained with Giemsa in the laboratory. As a rule, four such " snips " were made from each case from different parts of the body, before it was assumed that a case with negative findings was not one of onchocerciasis. Case K.154 may be cited to support the necessity for this: in this exceptional instance, twelve snips were done over a period of 3 weeks before one proved positive; this boy had active trachoma which was causing symptoms, but nummular opacities of the lower segment of the cornea were so typical that, although microfilariae were not seen in the anterior chamber or in conjunctival snips, a provisional diagnosis of onchocerciasis had been made on clinical grounds.

For cases seen during surveys, and for controlling those treated in schools, fresh skin snips were not examined, but the exudate from four superficial scarifications was smeared on a slide, dried, and examined later after staining

(Wanson, Henrard, and Peel, 1945), and again it was found necessary to make a number of smears in doubtful cases.

Living microfilariae can be demonstrated in the eye by mounting snips from the bulbar conjunctiva in saline on a slide and examining them immediately under the microscope. This method of examination has been used by Hissette and Ridley, amongst other observers. Hughes and Daly (1951), in a series of 32 cases of onchocerciasis with ocular lesions, found microfilariae in both aqueous and conjunctival snips in 21 cases, in the aqueous alone in seven cases, and in the conjunctiva alone in one case. In the present series, conjunctival snips were done in cases with suggestive clinical signs in whom microfilariae were not seen in the anterior chamber with loupe, ophthalmoscope, or slit lamp. In two of the three cases which showed microfilariae under these conditions, the organisms were seen in the anterior chamber at later examinations, and in the third case the corneal opacities were so severe as to make a clear view of the aqueous impossible by any method.

Aspiration of the anterior chamber with subsequent microscopic examination of the fluid (Bryant, 1935) was not done. The aqueous of one proved case trephined for secondary glaucoma did however show living microfilariae (Case H.2).

In two proved cases of onchocerciasis, upon which trephines were done for secondary glaucoma, no microfilariae were seen in sections of the excised pieces of sclera. The mathematical chances of finding embryos or parts of embryos in such sections are very small unless the infestation is heavy.

Ocular Manifestations

The clinical features reported are based on the findings in 319 proved cases of onchocerciasis: 206 African industrial labourers working in the vicinity of the lower reaches of the River Volta, 82 schoolchildren seen in schools in two riverine villages, and 31 patients who presented themselves at the Ophthalmic Department of the Gold Coast Hospital, Accra. The last group was drawn from all parts of the country, but in nearly all cases a history of having visited or lived near some part of the River Volta was obtained. Of these 310 cases, 109 (34.5 per cent.) showed some lesions of the eye which could be attributed to the onchocercal infection; this high incidence of eye lesions was found in spite of the fact that 288 of the cases were found in the course of surveys on subjects who were, judged by their own standards, fit. The lesions actually found are summarized in Table I.

TABLE I

TYPES OF EYE LESIONS FOUND IN PERSONS EXAMINED

Microfilariae in aqueous with ocular lesions	50
Microfilariae in aqueous without ocular lesions	44
Nummular keratitis, microfilariae in aqueous	37
Nummular keratitis, no microfilariae in aqueous	51
Iridocyclitis	15
Choroido-retinal degeneration	11
Optic atrophy	7
Lens sclerosis	11
Atrophy of iris with no other lesions	1
Total	227

The commonest ocular manifestation of onchocerciasis in this series of cases was the presence of microfilariae in the anterior chamber, frequently with no demonstrable lesion whatever in the eye. A rather similar observation was made by Scott (1945) in a report on African soldiers in the Cameroons. In 22 schoolchildren, in whom embryos were seen in the aqueous, all except one had visual acuities of 6/6 or better; in one whose visual acuity was 6/36 in each eye, there was early macular degeneration. The parasites could be seen with a slit lamp and corneal microscope, when they appeared as fine golden threads up to 50μ long, swimming freely in the aqueous; when seen with a 10 × loupe and oblique illumination, they appeared silvery in colour probably on account of the nature of the light. Alternatively, they could be seen fairly easily even in the less co-operative patients with an ordinary electric ophthalmoscope, using a plus 20 to 30 lens in the eyepiece. This technique, which is often more successful with nervous or illiterate patients, has been described elsewhere (Sarkies, 1951a). The existence of an invasive stage of the disease, when microfilariae are present in the eyes but before irreversible tissue changes occur, is of obvious practical importance. For example, in one patient (Case S.200), the anterior chamber seemed to be alive with embryos, but he had visual acuities of 6/5 in each eye and no lesions whatever. Two months later, during the course of treatment, a few nummular opacities of the cornea appeared and persisted, but these were insufficient to affect his vision. It was found during the course of prolonged observation and follow-up of cases with microfilariae in the aqueous, that the number of embryos (in fact their very presence when they were scanty) varied from hour to hour and from day to day; at one examination they would be present in one eye only and at the next in the other eye; there was no numerical relationship between microfilariae in the eye and the severity of the eye lesions.

Nummular opacities of the cornea due to the presence of dead or dying microfilariae in the substantia propria were reported by Ridley, and the microscopic appearances of this condition have been described by Hughes and Daly (1950). In the present series, ten cases showed microfilariae in the cornea with a surrounding area of infiltration which constitutes the nummular opacity. Nummular opacities were seen most commonly at the periphery of the cornea close to the limbus, though occasionally they were near the centre encroaching on the pupillary area. In their early stages they consisted of irregular infiltrations up to 0.5 mm. in diameter, during treatment they tended to become denser with a more regular edge, and finally the smaller ones disappeared while others left circular opacities usually situated in the deeper layers of the cornea. The clinical appearance of these lesions, when seen with a corneal microscope or a loupe, was found to be sufficiently typical to be diagnostic of ocular involvement with onchocerciasis; in every case in which they were seen, a skin snip was found to be positive for *mf. volvulus*, although embryos were not necessarily seen in the anterior chamber.

One other early ocular manifestation was noted; namely, a macular degeneration clinically similar to the senile form. This occurred in Patient K.2, the only schoolboy to show diminished visual acuity; there was a very slight patchy increase of pigment in the macular area, with intervening lighter areas, suggesting that the sclera was shining through an atrophic retina. It seems likely that this condition would progress to the fully developed picture described by Ridley, but unfortunately no case was seen which showed an intermediate stage. Of the advanced choroido-retinal lesions, only one resembled Ridley's description; in the others the appearance was not specific. Disseminated choroido-retinitis, isolated peripheral patches of choroido-retinitis, and diffuse atrophy of the chorio-capillaris were all seen, with varying degrees of optic atrophy.

Two factors which were constant in all the advanced fundus lesions were a marked increase in pigment, and a perivascular cuffing of the retinal vessels extending from the point where they emerge from the optic disk to a distance of two or three disk diameters towards the periphery of the fundus. This appearance, thought to be due to fibrous thickening of the vessel wall following cellular infiltration, was seen in seven advanced cases of onchocerciasis either in one or in both eyes; it is worthy of note that in any eye which showed this particular appearance the visual acuity was less than counting fingers at one metre. Case H.44, which is fully described later, showed this perivascular cuffing very clearly in the right eye, in which the visual acuity was reduced to recognition of hand movements (Fig. 1), whereas in the left eye, in which the vessels were normal, the vision was 6/12. Hughes and Daly (1950) demonstrated sections of a blind eye excised from a patient with onchocerciasis; that was an advanced case and sections stained with Van Gieson show marked thickening of the walls of the retinal vessels in the region of the optic disk (Figs 2 and 3). While it would be more conclusive still to reproduce sections of an eye of which the fundus had been seen, the African's reluctance to part with even a blind, painful eye made the obtaining of sections impossible. However, the presence of a fibrous thickening of the walls of the retinal vessels in sections of an eye known to be affected by onchocerciasis does accord with the clinical findings seen in other cases *in vitro*.

It was found impossible to establish any definite symptomatology for early ocular onchocerciasis. Even in a literate group of 224 schoolchildren, most of whom were between 12 and 18 years of age, such symptoms as were found, were at least as common amongst those who showed no signs of the disease whatever, as amongst those who had microfilariae and lesions in the eyes; the latter also frequently denied having any trouble. The tolerance of Africans is high in this respect, and this observation does not necessarily apply to other races.

Diagnosis.—Early recognition of ocular onchocerciasis is of vital importance, as it is in this stage that treatment will offer hope of success. In this series, the

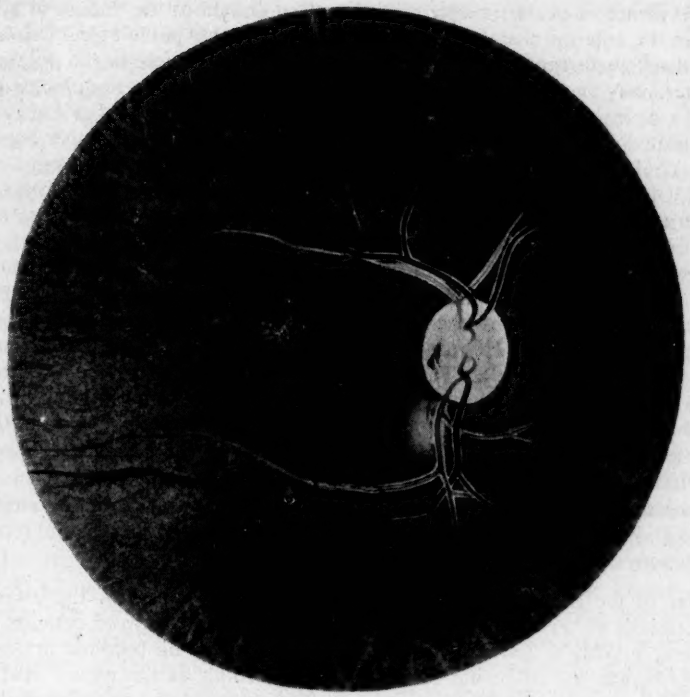

FIG. 1.—Copy of oil sketch made by the writer, from right fundus of Case H.44, showing typical perivascular cuffing and optic atrophy.

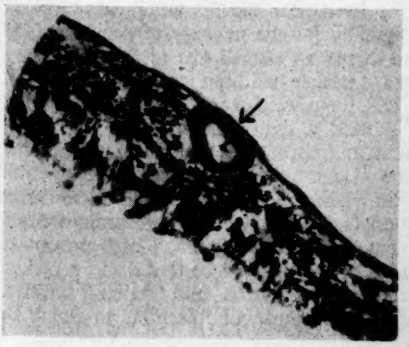

FIG. 2.—Section of retina from a case of onchocerciasis (Van Gieson × 146) cut near optic disk.

FIG. 3.—Section from same eye as in Fig. 2 (Van Gieson × 70).

earliest evidence of ocular involvement was often limited to the finding of microfilariae in the anterior chamber without any demonstrable pathological lesion; in others, there were scanty patches of nummular keratitis which, in the opinion of the writer, may be regarded as diagnostic if accompanied by nodules or presbydermia, or by laboratory evidence of the disease. It was found that a history of having visited an endemic area could often be elicited, but on the other hand no reliance could be placed on a denial of this in the class of patient most often affected. Repeated clinical and laboratory examinations were often necessary to establish a diagnosis. Microfilariae in the anterior chamber are almost certainly those of *O. volvulus* and attempts to find embryos of *D. streptocerca* have proved unsuccessful (Sarkies, 1951). Seven cases in this series, which showed microfilariae in the aqueous at the first examination in the absence of any other ocular or systemic manifestations of onchocerciasis, ultimately showed positive skin smears.

Therapeutic tests with Hetrazan were suggested as a confirmatory diagnostic measure by Ridley (1950). This technique has undoubted value, especially outside the tropics when infection with other filariae can be excluded; in lightly infected cases, however, the allergic reaction which occurs may be so mild that it cannot be distinguished from that which occurs with *Loa loa* or *Wuchereria bancrofti*, either of which may be coexistent with *O. volvulus*.

Diagnosis of infection with *O. volvulus* rests in demonstrating the microfilariae in the skin, but recognition of ocular involvement necessitates patient and repeated examinations of the eyes by all available methods.

Course of the Disease.—Very little is known of the course of the disease in onchocerciasis either with or without treatment: this is because patients come from remote villages, and when they return home follow-up becomes impossible. For this reason the following case is worth recording as the patient had been examined 5 years earlier by the Command Ophthalmologist on being invalided from the army, and brief notes were available from the documents of his medical board.

Case H.11, K. A., a farmer, aged 25, who lived near the R. Volta, was seen on January 12, 1951, during a review of his disability for the ministry of pensions. On examination he had slight presbydermia, and there was a small scar in the midaxillary line over the right seventh rib, where, he stated, a nodule had been removed. His visual acuity was 6/36 right and counting fingers left, there were scanty microfilariae in the aqueous of both eyes; the right fundus showed a clearly circumscribed patch of choroiditis with gross pigment aggregations in the upper nasal quadrant, and in the left there was a similar lesion involving the macula; there was optic atrophy with atrophic cupping of the disk on both sides. Skin smears showed numerous microfilariae of *O. volvulus*. A copy of this patient's original medical board proceedings dated October, 1945, showed that exactly similar patches of choroiditis had been present at that time, and there had been no change in his visual acuity since that date; a nodule containing an adult onchocerca had been removed and his skin snip had been positive. The pensioner stated that he had been given "a course of injections in the V.D. Department" before his discharge from the army.

The retinal lesions in this case were not typical of onchocerciasis and it is doubtful if they were in fact the result of this disease. The Command Ophthalmologist had reported "Bilateral choroido-retinitis possibly due to onchocerciasis", having evidently had similar doubts. This was therefore a patient with

onchocerciasis known to have had the infection for at least 5 years without any definite deterioration in his condition.

Treatment.—Various drugs have been used in the treatment of onchocerciasis, but with two exceptions few have given much promise of success. Van Hoof and others (1947) found that " Antrypol " B.P.C. Suraminum, other proprietary names Bayer 205, Naphuride, and Germanin) showed a filaricidal effect against both the adult onchocerca and the microfilaria. Hewitt and others (1947) reported striking results using " Hetrazan ", one of the piperazine derivatives, against other filarial infections in the cotton rat and dogs. Since then Burch (1949) has compared the effect of these drugs and was able to conclude that Antrypol was the more effective against both microfilariae and adult *O. volvulus*.

Considerable difficulties have been encountered in attempting treatment of African patients in this series of cases. In the first place, only a few were willing to come into hospital for treatment; the occurrence of side-reactions of any severity acted as a powerful deterrent to their continuing treatment, and conversely, in a number of cases, the absence of any early and dramatic signs of improvement resulted in the patient losing interest and ceasing to attend. It was only possible to collect 33 cases, all of which showed ocular involvement, which were treated with Antrypol alone or with a combination of Antrypol and Hetrazan. Two cases complicated by secondary glaucoma were treated surgically by trephining.

Five cases were treated primarily with " Banocide ", another piperazine derivative, the dosage being 1.35 g. daily for 20 days; this resulted in a minimum dosage of 367 mg./kg. body weight, which is a good deal higher than that employed by Burch. In all five cases microfilariae had disappeared from the aqueous within 8 days of starting treatment: in one case, skin smears were positive throughout treatment; in the remaining four, the skin had become clear of embryos by the 10th to the 15th day but was showing embryos once again within 3 weeks of completing treatment; of these four, two had numerous microfilariae again visible in the aqueous within 3 weeks of completing their course of treatment. All these cases showed side-effects in the course of treatment, the main change in the eyes being a marked ciliary injection starting on the first day of treatment and clearing by the sixth day; one case which showed evidence of a localized retrobulbar neuritis is described elsewhere (Case S.200). Allergic skin eruptions, though they did occur, were not so severe as to necessitate stopping treatment, as all were hospital cases. The comparative mildness of these side-reactions may have been due to the fact that Anthisan 0.2 mg. was given with each dose of Banocide for the first few days. Four of the cases were subsequently treated with Antrypol, and it was found that side-reactions were noticeably less severe than in cases which had not previously had Banocide.

In all, 32 cases of onchocerciasis were treated with Antrypol; these had microfilariae in the anterior chamber, with or without other clinical lesions; 1 g. was given intravenously once weekly for 8 to 9 weeks. Four of these cases had previously received a full course of Banocide, 22 received Antrypol alone, and six were given 6.75 g. Hetrazan after completing a course of Antrypol. The periods over which it was possible to follow the cases varied; one was seen 9 months after beginning treatment. The effects of Antrypol on the eyes were remarkably constant. It was found that the microfilariae disappeared from the aqueous between the fourth and sixth weeks of treatment. At about this time, in

twenty of the cases, there was evidence of a mild iridocyclitis; fine deposits of iris pigment appeared on the anterior surface of the lens or festooned on the threads of persistent pupillary membrane which are commonly seen in African eyes. Ciliary injection was slight if it occurred at all, and no patient complained of any ocular symptoms in the course of treatment. Patches of nummular keratitis appeared for the first time in twelve of the cases, during the fourth week of treatment, and became more numerous in nine other cases in which they had been present before. Pruritus and allergic skin eruptions occurred in every case during the fifth or sixth week of treatment, but in only one case were they so severe as to warrant admission to hospital ; in general the side-effects were less severe than with Banocide. Five cases developed albuminuria but this cleared up after temporary cessation of treatment. Anthisan was given only after the onset of skin manifestations.

TABLE II

EFFECTS OF TREATMENT ON DEGREE OF INFESTATION

Case No.	Treatment	Initial Skin Smears	Week of Treatment						3 Months after Completion		Antrypol mg./kg.
			5th		7th		9th				
			Eyes	Skin	Eyes	Skin	Eyes	Skin	Eyes	Skin	
S.176	X	+++	O	P	O	O	O	O	P	+	120
S.200	X	+++	O	P	O	P	O	P	O	+	170
H.26	X	+	O	+	O	+	O	+	O	+	106
H.27	X	++	P	P	O	P	O	O	—	—	169
K.59	Y	+	O	O	O	O	O	O	O	O	133
K.72	Y	+	O	O	O	O	—	—	—	—	150
K.160	Y	++	O	P	O	O	O	O	O	+	161
S.174	Y	+	O	P	O	O	O	O	O	O	158
S.180	Y	+	O	P	O	O	O	O	O	O	127*
S.192	Y	+	O	P	O	P	P	O	O	O	137
K.2	Y	+	P	P	—	—	P	P	—	—	26
K.64	Y	+	P	O	O	P	O	O	—	—	121
K.121	Y	++++	P	P	—	—	—	—	—	—	31
S.189	Y	+	P	P	P	—	—	—	—	—	62
S.190	Y	++	P	P	P	P	—	—	—	—	143
S.227	Y	+++	P	P	—	—	—	—	—	—	38
H.2	Y	++	O	P	O	P	O	P	O	+	153†
H.4	Y	+++	P	P	P	P	P	++	—	—	140
H.5	Y	++	P	P	P	P	P	+	—	—	147
H.7	Y	++	O	P	O	P	O	O	O	O	117
H.16	Y	++	O	P	O	O	O	O	—	—	122†
H.20	Y	+	O	O	O	O	O	O	O	O	101
H.28	Y	+++	P	P	O	P	O	P	O	+	163
H.29	Y	+	O	P	O	O	O	O	O	O	114
H.6	Y	++	O	P	O	P	—	—	—	—	69
H.10	Y	+	O	+	—	—	—	—	—	—	43
K.158	Z	+++	P	P	P	P	P	++	O	O	169‡
K.103	Z	+	P	P	P	P	O	O	O	O	146‡
K.159	Z	+++	P	P	P	P	O	P	O	+	138‡
K.154	Z	++	O	P	O	P	O	+	O	+	37‡
H.3	Z	+++	O	P	O	P	O	O	O	O	161‡
H.69	Z	++++	P	P	O	P	O	++++	O	+	167‡

X = Antrypol preceded by full Banocide course.
Y = Antrypol alone.
Z = Antrypol followed by short course of Hetrazan.
P = *Mf* present not counted.
O = No *mf* seen.
*Trachoma.

\+ = 1–20 *Mf* in thick drop.
++ = 20–40 *Mf* in thick drop.
+++ = 40–100 *Mf* in thick drop.
++++ = 100 *Mf* in thick drop.

† Bilateral glaucoma.

‡ Skin negative in 10th week of treatment.

No case showed deterioration in visual acuity during treatment with Antrypol; conversely, there was no improvement in the vision of any patient who showed loss of visual acuity due to retinal lesions. The effects of treatment on the degree of infestation with onchocerciasis are summarized in Table II.

In the course of observation an attempt was made to estimate the intensity of infection at different stages of treatment. In all cases the numbers of microfilariae seen in a skin smear were counted before starting treatment, and counts were made again in some cases at the end of the course of Antrypol and at the final examination in all those cases which could be followed for 3 months. This is obviously a very rough guide, but as far as possible smears of a constant size were made.

At the end of treatment, ten out of 25 patients still had positive skin smears and five still had microfilariae in the aqueous; 3 months after finishing treatment, nine out of twenty patients had positive skin smears, one showing microfilariae in the aqueous, and of these two had been free previously and had relapsed. All cases showed an appreciable reduction in the number of parasites in skin smears either during or after treatment, and in every case but one the parasites had disappeared from the eyes. The administration of Hetrazan after Antrypol caused a temporary disappearance of the embryos in those cases which still had positive smears. In eight cases, the serum Antrypol was estimated at varying periods after completing treatment (Table III). These results show that relatively high concentrations of the drug may be expected in the blood for periods up to 3 months, but it was not possible to correlate the level of the serum Antrypol with the presence or absence of parasites in skin smears.

TABLE III

ESTIMATION OF SERUM ANTRYPOL AFTER COMPLETING TREATMENT

Case No.	Antrypol mg./kg.	Weeks since last Injection	Serum Antrypol mg./100 ml.	Skin Smear	*Mf* in Eyes
K.59	133	10	8·0	Negative	Nil
K.154	37	10	5·5	Positive	Nil
K.158	159	10	10·0	Negative	Nil
S.174	158	11	9·6	Negative	Nil
S.176	120	10	9·5	Positive	Present
S.180	127	14	6·0	Negative	Nil
S.200	170	10	7·6	Positive	Nil
H.69	167	8	4·7	Positive	Nil

In general, it may be deduced that with the dosage employed, damage to the eyes in individual cases of onchocerciasis may be prevented or arrested by means of Antrypol and that this effect lasts longer than that of the Banocide group of drugs: the administration of Banocide or Hetrazan after Antrypol is of value in those cases which still have strongly positive skin smears at the end of a course of Antrypol. The easier method of administration, the less severe side-reactions, and the better retention in the tissues make Antrypol the drug of choice, especially where there is a likelihood of re-infection. The fact that infection persisted in nearly 50 per cent. of cases 3 months after completion of treatment makes it seem unlikely that either Antrypol or Banocide is a cure for onchocerciasis, and in

order to prevent visual loss or blindness it is necessary to keep cases under repeated observation, so that at any sign of recurrence of microfilariae or actual lesions in the eye, further treatment can be given. There is some evidence to show that the administration of Anthisan with filaricidal drugs to some extent ameliorates the allergic side-reactions.

Surgical Treatment.—Surgical treatment in cases of onchocerciasis in this series was limited to the relief of ocular hypertension in two cases complicated by secondary glaucoma.

Case H.16, Y. O., a farmer, aged 68, complained of increasing loss of vision for about 4 months, with a vague history of "pains in the eyes" and skin irritation. On examination there was presbydermia excessive for his age, visual acuity was reduced to recognition of hand movements, and there was marked sclerosis of both lenses. The tension as recorded by a Schiötz tonometer was 35 mm. Hg in the right eye and 40 mm. Hg in the left; the average diurnal variation over 3 days was 9 mm., and the tension after eserine fell to 28 mm. in the right eye and 32 mm. in the left. Skin smears showed numerous microfilariae of *O. volvulus*, but there were no microfilariae in the anterior chamber or in conjunctival snips. On October 11, 1950, he was given eserine drops twice daily and Antrypol 1 g. weekly. On November 18, 1950, the tension was still high and it was evident that he was not using the eserine regularly; he was therefore admitted to hospital and the eyes were trephined, allowing a week between operations; there was no undue reaction after operation. When last seen on January 3, 1951, the eyes were quiet, the tension being 20 mm. Hg right and 24 mm. Hg left, both trephines were draining well, and the visual acuity was unchanged. He had finished his course of Antrypol and skin smears were negative for microfilariae. Sections of the scleral disk and the excised slip of iris showed no microfilariae, nor did the aqueous which escaped at operation. In the right eye projection was fair, and the patient was advised to return later for cataract extraction.

Case H.2, K. W., a farmer, aged 26, complained of dimness of vision, which he said had been getting worse for about a year; he denied ever having had any pain in the eyes. On examination he was found to have presbydermia but no nodules. His visual acuity was reduced to hand movements in the right eye and 6/36 in the left, but as he was illiterate these must be regarded as approximations. He had a few nummular opacities in both corneae, the right eye showed numerous cells in the aqueous with a few fine cellular deposits on the posterior corneal surface, and in the left eye there were a few definite pigmented keratic precipitates; no microfilariae were seen, but conjunctival biopsies from both eyes showed microfilariae and there were numerous *m. volvulus* in skin smears. The pupils were small and reacted sluggishly to light, the tension was 62 mm. Hg Schiötz in both eyes, and both optic disks showed deep glaucomatous cupping. He was admitted to hospital on February 7, 1951, and treated with atropine and local heat; 3 days later the tension had fallen to 40 mm. Hg in the right eye and 44 mm. Hg in the left. This level being maintained, on February 25, 1951, the left eye was trephined under retrobulbar anaesthesia, and a similar operation was done on the right eye 4 days later. In each case the post-operative course was uneventful. He had been given Antrypol by injection from the outset, and it is interesting that microfilariae were seen for the first time in the aqueous during the fourth week of this treatment. After the completion of his Antrypol course on May 14, 1951, the aqueous was again clear and the conjunctival and skin biopsies were negative; the trephines were draining well and the tension was 22 mm. Hg in the right eye and 24 mm. Hg in the left. The visual acuities were 6/60 in the right eye and 6/24 in the left.

The treatment of glaucoma occurring as a complication of onchocerciasis poses some interesting problems. The mechanism of the aetiology of glaucoma in this

disease is by no means clear. In Case H.2 it seems probable that the hypertension was secondary to uveitis caused by the presence of *mf. volvulus* in the anterior segment of the eye, and the presence of marked glaucomatous cupping suggested that the condition had been present for some considerable time; if this hypothesis were correct, then the logical approach was to treat the uveitis with mydriatics and heat, at the same time eliminating the exciting parasite. It has been shown, however that the known methods of treating onchocerciasis are themselves liable to cause a mild iridocyclitis which could be expected to aggravate the glaucoma still further. In Case H.16, although there was no evidence of uveitis and microfilariae were at no time demonstrated in the eye, onchocerciasis as an exciting cause of glaucoma cannot be excluded, since it has been shown that vascular and other lesions of the posterior segment occur in onchocerciasis in the absence of demonstrable microfilariae. In both cases, therefore, medical treatment was applied on general principles with partial success. Antrypol was chosen as a filaricide in preference to one of the piperazine derivatives, as its action was known to be slower and the allergic side-reactions less severe.

The principal indication for surgical intervention was the necessity for prevention of further visual loss due to prolonged ocular hypertension; but in dealing with the rural population of tropical countries, other factors have to be taken into account. Elliot (1920), after experience in India, pointed out that surgery was often necessary in cases which would be treated conservatively if only patients could be followed-up. Trephining was the operation of choice, as it has been found that manipulation of the iris during iridencleisis in deeply pigmented African eyes often results in dense deposits of pigment on the anterior surface of the lens, which in itself causes a lowering of the visual acuity. By gentle pressure on the prolapsed knuckle of iris with a repositor after completion of the trephine, the aqueous can be released slowly and the risks of sudden decompression are avoided; further, any pigment which is released during this stage and during the subsequent iridectomy does not find its way into the anterior chamber.

Riboflavine in Onchocerciasis.—While working in the Northern Territories of the Gold Coast, Saunders (1929) noticed the presence of onchocerciasis, but he attributed the blindness which he found in the area to malnutrition rather than to that disease. Fitzgerald Moore (1930–1936) described optic atrophy associated with vitamin B deficiencies in schoolboys in Nigeria. This work was done in a district subsequently shown by Nwokolo (1950) to be endemic for *O. volvulus*. Recently, the present writer saw a case of onchocerciasis in which there were numerous microfilariae in the anterior chamber and in snips from the conjunctiva but no other demonstrable lesions, and the visual acuity in this case improved from 6/12 to 6/5 with riboflavine by mouth in dosages of 9 mg. daily for 21 days. Since then an attempt had been made to collect a series of literate cases of a similar nature; three literates have been seen, and also two illiterates whose intelligence enabled the visual acuity to be assessed fairly accurately; these cases are reported more fully below.

Case H.26, E. T., a lorry driver, aged 25, who had one year's service in the army, complained of " soreness of the eyes for two weeks "; he had visited many areas known to be endemic for onchocerciasis. Examination showed numerous active microfilariae in the anterior chamber, and there was a patch of presbydermia over right scapula, but no nodules were found. A conjunctival snip showed microfilariae, and stained skin

smears showed microfilariae of *O. volvulus*, and of *D. streptocerca*. Visual acuity was 6/12 in both eyes and there were no other abnormalities.

He was given riboflavine tablets by mouth (9 mg. daily) and after 14 days his visual acuity was 6/6 in both eyes; after a further 7 days' treatment vision had improved to 6/5 in both eyes, though microfilariae were just as numerous in the anterior chamber and laboratory findings were still positive.

Case H.27, E. N., a schoolboy, aged 14, complained of "black wormlike objects" obscuring his vision. Visual acuity was 6/9 in both eyes; there were numerous microfilariae in both anterior chambers, two faint nummular opacities in the left cornea and one in the right, and a few fine pigmented keratic precipitates in the left eye only; the fundus was normal and there was no refractive error.

He was given 10 mg. riboflavine per day intravenously for 21 days, and at the end of this time vision was 6/5 in both eyes. Examination with ophthalmoscope and slit lamp showed no change in the eye condition.

This patient was seen 3 months later, after a course of Banocide, again complaining of loss of distant vision. He had microfilariae in the anterior chamber, skin snips were positive, and his vision was down to 6/9 in both eyes. On this occasion he was given riboflavine 9 mg. per day by mouth and after 18 days vision was 6/5 in both eyes. He then had a course of 8 g. Antrypol, and a month after this the eyes were clear and repeated skin snips were negative.

Case S.200, A. K., a schoolboy, aged 14, was discovered during the course of a survey to have presbydermia and five typical subcutaneous nodules. He was free of symptoms, but examination of his eyes revealed more numerous microfilariae in the anterior chambers than the writer has ever seen in any other case of onchocerciasis; his visual acuity was 6/5 in both eyes, there were no corneal opacities, and careful examination showed no other clinical manifestations, though smears from the skin were full of microfilariae of *O. volvulus*. He gave a history of having lived all his life in a village on the R. Volta.

He was admitted to hospital on November 9, 1950, and was given Banocide 450 g. with Anthisan 2 mg. As he was an intelligent boy, visual fields were estimated and there were no abnormalities. After one day of treatment he had slight injection of the bulbar conjunctiva and a fairly well marked urticarial rash. On the fourth day the rash was less, he had no microfilariae in the eyes, and skin snips were negative; both optic disks showed a slight vascular congestion but visual acuity was still 6/5 in both eyes. On the fifth day one microfilaria was seen in the right anterior chamber; the patient felt better, but there were fine pigment deposits on the anterior surface of the lens on the right side. On the seventh day the skin had cleared, leaving a fine branny desquamation, but visual acuity in the left eye was only 6/9, that in the right eye being 6/5; both disks showed the same vascular congestion, and investigation of the central fields showed a small paracentral scotoma in the left eye to a 1/1,000 white target; the blind spots were not enlarged. At this point, 10 mg. riboflavine were given intravenously daily and the Banocide was continued at the same dosage. Two days later the visual acuity was again normal, the scotoma had disappeared, and no microfilariae were seen in either eyes or skin. After 21 days, during which the patient had received 28.35 g. Banocide (0.301 g./kg. body weight), he was discharged from hospital; there were no microfilariae in the eyes or skin, vision was normal, and no nummular opacities were present, but there were a few fine pigment granules on the anterior surface of the lens in both eyes.

Case K.2, J. Y., schoolboy, aged 18, found during a survey, complained of loss of distant vision for a period of 10 years, having lived in a known onchocercal area all his life. His skin was normal and he showed no nodules. Distant vision was 6/36 in both eyes, and he could read only J8. Both eyes showed a few embryos in the aqueous,

there were numerous nummular opacities of both corneae, examination of the fundus showed a fine degree of pigmentary mottling of the macula on both sides, which closely resembled senile macular degeneration, and the optic disks were normal. *Retinoscopy was normal and the vision did not correct.*

The patient was given 9 mg. riboflavine daily by mouth as an out-patient, and when seen a week later his vision had improved to 6/24 in both eyes; another week later there had been no further improvement, and, as he was an unreliable patient, he was admitted to hospital and given riboflavine 10 mg. daily intravenously to ensure that he got his treatment. After a week of intravenous riboflavine, the vision had improved to 6/18 in both eyes, when the boy discharged himself from hospital to attend some festival in his village. When seen 7 weeks later he had embryos in the aqueous, positive skin smears, and numerous nummular opacities of the cornea, but his vision remained 6/18 in both eyes. He has now left school and has not been seen since.

Case H.6, M. M., labourer, aged 24, complained of loss of vision which had come on rapidly during the preceding fortnight. On examination vision was 6/36 in the right eye (illiterate " E "), and reduced to counting fingers at 1 metre in the left eye. There were signs of a chronic plastic iridocyclitis which appeared to be of some considerable duration, and in the right eye the fundus showed a disseminated choroiditis with peripheral patches of bone corpuscle pigmentation, perivascular cuffing of the central parts of the retinal vessels, and optic atrophy. He had a marked presbydermia and there was cheilosis and papillary hypertrophy of the tongue. No microfilariae were seen in the aqueous or in conjunctival biopsies, but skin smears showed numerous microfilariae of *O. volvulus.*

This patient was treated with 10 mg. riboflavine intravenously once daily, and atropine drops 1 per cent. to the left eye; after one week the vision had improved to 6/12 right and 4/60 left, and the cheilosis and sore tongue had cleared. The patient was not able to do accurate visual fields, but to confrontation there was a marked restriction of the right peripheral field. There was no further improvement.

Case H.44, B. B., labourer, aged 22, was first seen complaining of loss of vision and of night blindness which had increased during the last 4 months. Visual acuity in the right eye was reduced to hand movements and in the left to 6/12; the corneae were free of any opacities but scanty microfilariae were seen in the aqueous. The right fundus showed an advanced degree of optic atrophy with well marked cuffing of the retinal vessels as they emerged from the disk, and there were patchy areas of retinal degeneration with marked macular involvement. The left fundus showed some pallor of the optic disk, but was otherwise normal apart from a slight increase in pigmentation, which is difficult to assess in Africans. The patient could not co-operate sufficiently to plot the visual fields, though to confrontation they seemed to be reduced almost to fixation on the left side. It was very noticeable that, although he could see well in daylight, as soon as he went into a dim light he was unable to move around the room. Skin snips and smears showed an extremely heavy infestation with onchocerciasis, though there was only a moderate degree of presbydermia.

He was given 10 mg. riboflavine intravenously for 16 days, at the end of which time vision in the left eye had improved to 6/6; there was no improvement in the right eye.

Case H.3, T. K., tailor's apprentice, aged 23, complained of photophobia and lacrimation for some months. He had lived all his life in a riverside town and had attended school there. His visual acuity was 6/5 in both eyes, there was slight vascular injection of the bulbar conjunctiva of both eyes and evidence of marked photophobia. Copious lacrimation was elicited during examination of the eyes. There were numerous peripheral nummular opacities of the corneae, most of which were irregular in outline and in a state of active development, many showing dead microfilariae in the centre of the areas of infiltration; scanty living microfilariae were seen in the aqueous, and both fundi

were normal. The skin showed marked presbydermia and there was one nodule over the coccyx; skin smears showed a heavy infestation with *O. volvulus*.

Riboflavine 6 mg. by mouth thrice daily for 14 days had no effect whatever on the symptoms or signs in the eyes.

From the foregoing it is evident that the administration of large doses of riboflavine, either by mouth or by injection, produces functional improvement in cases of onchocerciasis when the visual acuity is diminished as a result of lesions of the posterior segment, though not in corneal lesions. This improvement is most marked in early cases, though some effect may be expected when there is retinal damage and early optic atrophy; in some cases improvement is limited to one eye in which the lesion is less advanced. There is no conclusive evidence to show at which point in the visual arc riboflavine acts; the clinical findings, supported by pathological evidence from advanced cases, suggest that the lesion may be primarily vascular, either in the retina or in the optic nerve. Stannus (1944) suggested that stasis or " capillary dysergia " may result from riboflavine deficiency, and Axelrod and others (1942) showed experimentally that riboflavine takes part in tissue cell metabolism; a reaction specific to riboflavine and unaffected by biotin or pantothenic acid.

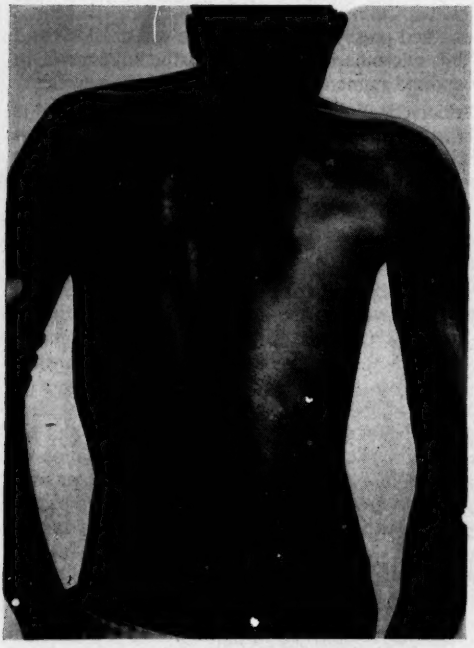

FIG. 4.—Limited presbydermia in African with onchocerciasis, localized around a subcutaneous nodule in the lumbar region.

One of the cases described above (H.6) showed other manifestations of riboflavine deficiency, a condition which can be expected in the Gold Coast where the intake of animal protein is low. Such animal protein as is taken often consists in sun-dried fish, and all food is usually exposed to strong sunlight for considerable periods, a factor shown by Williams and Cheldelin (1942) to reduce the riboflavine content to a considerable extent. In another case (S.200) there was evidence of a limited optic neuritis developing during treatment with hetrazan; the pathological lesion here was probably similar to the localized cellular infiltration around dead microfilariae in the optic nerve (Hughes and Daly, 1950).

It seems probable that other factors may also play a part. Colbourne and others (1950) showed that the Gold Coast villager, even in the more prosperous agricultural areas, lives in equilibrium with several parasites, such as those of malaria, schistosomiasis, and hookworm; it may be that when

a further infection with onchocerciasis becomes too heavy, the host-parasite balance is disturbed and lesions of malnutrition result. In cases of this nature, riboflavine or treatment of other intercurrent disease might be equally effective. Therefore, in the absence of scientific proof of a true riboflavine deficiency in cases of onchocerciasis, for the time being this line of treatment must remain largely empirical.

Comment

The early signs of ocular involvement in onchocerciasis are so slight that any estimates of the incidence of this complication made without careful examination to exclude the presence of microfilariae in the eye must be low; this fact probably accounts for the considerable variations in published figures. In the present series of 319 cases of proved onchocerciasis, 14 per cent. showed microfilariae in the eye with no ocular lesions, and 16 per cent. showed nummular opacities which were often very scanty; it must be remembered that the great majority of these cases were mild ones but there is no means of knowing how many would ultimately go blind. Scott who examined the eyes of fit soldiers from the Cameroons also found a high proportion of cases with microfilariae. It seems likely therefore that some other factor, such as malnutrition or intercurrent disease, may play a part in the onset of actual lesions.

While it appears that damage to the eyes can be arrested, or in early cases prevented, by the use of Antrypol, it is extremely doubtful on the evidence of this series that this effect is permanent. There is some indication for the use of one of the piperazine derivatives after completion of a course of Antrypol in those cases in which skin smears still show embryos, but in all cases a prolonged follow-up is necessary to avoid damage to the eyes in the event of relapses. Glaucoma occurring in the course of ocular onchocerciasis requires treatment on general principles.

The above measures offer reasonable hope of preventing blindness in individual cases but are not applicable on a wide scale in rural tropical areas where the incidence of the disease is highest. A reduction in transmission could be expected from treatment of one hundred per cent. of the population in such areas by reducing the infectivity of the human host. For work of this nature, however, a drug is needed which does not cause severe side-reactions and is reasonably cheap, and the administration of which can safely be left in the hands of semi-skilled assistants. None of these conditions is fulfilled by antrypol or by the piperazine derivatives. In limited areas the incidence of the disease has been successfully reduced by eradication of the *Simulium damnosum* vector with D.D.T.; Garnham and McMahon (1947) have reported favourably on this method from Kenya, and it has also been used by Wanson, Courtois, and Lebied (1949) in Leopoldville.

Little is known of the life history of the causative parasite, e.g., the development of the mature embryo from the time of its injection into the tissues of man until it forms a fully mature adult producing numerous microfilariae;

when more is known it may be found that at some stage in this process it is susceptible to treatment.

Summary

A brief review is given of the general and ocular findings in onchocerciasis as previously described in the literature, followed by a description of the ocular manifestations as they were seen during the investigation of 319 cases in the Gold Coast. The great majority of these cases were mild ones and emphasis is laid on the early signs of ocular involvement which occur before irreversible damage is done to the eyes. Confirmatory diagnostic measures are discussed in the light of personal experience.

Cases are described suggesting a vascular origin for the lesions seen in the posterior segment of the eye; this finding is supported by pathological evidence and the clinical appearance is considered to be specific.

Results are summarized of filaricidal therapy in 33 cases with ocular involvement treated with Antrypol, or with a combination of Antrypol and one of the piperazine derivatives. The drugs are shown to have at least a palliative effect, and no dangerous side-reactions occurred in the eyes during treatment.

Two cases complicated by a secondary glaucoma are described in full and their medical and surgical treatment discussed.

The effect of riboflavine administration in cases with visual loss and early optic atrophy is described. While no indication of the mechanism could be found, the beneficial effect of this form of therapy in six cases showing those features is demonstrated.

I wish to thank Dr. R. L. Cheverton, D.M.S. Gold Coast, for permission to carry out this investigation and to publish the results.

Dr. M. H. Hughes of the Medical Research Institute, Accra, has carried out many of the laboratory investigations quoted and has very kindly allowed me to reproduce photomicrographs of some of his slides; further he has been an unfailing source of invaluable advice.

I also have to thank Mr. J. B. Johnston of the West African Council for taking the clinical photograph reproduced in Fig. 3, and Mr. Hepple for the photomicrographs in Figs 2 and 3.

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PACCHIONIAN-LIKE BODIES IN THE HUMAN CANAL OF SCHLEMM*

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As long ago as 1876 Key and Retzius suggested that the canal of Schlemm was like a dural venous sinus, and Rochon-Duvigneaud (1892) was insistent on this point. Also, Wegefarth (1914), in experiments on the cerebro-spinal fluid, which ran parallel with those of Weed (1914), showed that Pacchionian-like bodies occurred in Schlemm's canal in cats, dogs, rabbits, and monkeys. Since, however, this way of thinking is by no means universal, this article attempts to show that Pacchionian-like bodies occur normally in the canal of Schlemm in man.

FIG. 1.—Section of Pacchionian body. Note two kinds of connective tissue. *Zenker.* Mallory's triple stain. × 184.

Now haematoxylin and eosin, and van Gieson, are invaluable stains, but one may be led completely astray if one employs them for demonstrating *very fine* connective tissue fibrils. Thus the vessels of the iris are classically described as having thick walls of almost hyaline appearance, whereas with Mallory's triple stain after Zenker fixation they are shown to consist in fact of extremely fine connective tissue fibrils.

For the same reason, I would suggest, a great deal of misconception still exists about the connective tissue content of the Pacchionian bodies and the structure of the inner wall of the canal of Schlemm.

A Pacchionian body is formed, as Luschka (1852) showed, by the growth of a normally occurring arachnoidal villus through the dura into the overlying venous sinus or lacuna lateralis. A Pacchionian body is thus at its commencement the same as villus, but

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where macroscopic usually consists of several lobules and villi covered by a common endothelial membrane and possessing a common stalk. The Pacchionian body is usually covered by a layer of flattened cells containing large nuclei and lightly staining protoplasm (Le Gros Clark, 1920), but the endothelium may consist of two or many layers (Fig. 1). The connective tissue content of the Pacchionian body is variously described, but usually, I think, according to the appearance seen in sections stained with haematoxylin and eosin or van Gieson. With Mallory's triple stain the following picture appears: directly under the endothelium is a layer consisting of exceedingly fine fibrils while deeper are much coarser fibres which are also much more loosely packed (Fig. 1).

The relative size of the fibres of these two characteristic types of connective tissue may be judged from the fact that a $\frac{1}{6}$ objective is required for the fine ones, while the coarser ones are seen with a $\frac{2}{3}$ objective and even with a much lower power. The fine fibres are the continuation of the arachnoid, the coarser ones of the subarachnoid trabeculae.

The villi may be covered by a single layer of cells, but in some these form a multi-layered cap (Fig. 2); beneath the endothelium is the layer of fine

FIG. 2.—Arachnoidal villus. Note multi-layered nuclear cap, also fine fibrils below endothelium and coarse subarachnoid trabecula forming core. × 265.

FIG. 3.—Arachnoidal villus. Note fine fibrils in projection and coarse fibrils at base. × 169.

fibrils, while the core is formed of the coarser subarachnoid trabeculae, or the whole villus may consist of the fine fibrils while the coarser ones run across the base (Fig. 3). There are, thus, two types of arachnoidal villi, a fact, incidentally, which I have not found mentioned in the literature.

The inner wall of the canal of Schlemm is usually flat but it may project into the lumen-like villus (Fig. 4), and may indeed reach the outer wall. It is usually lined by a single layer of cells, which are like those covering the Pacchionian body, but it may be in two or more layers, and may even form a multi-layered cap (Fig. 4).

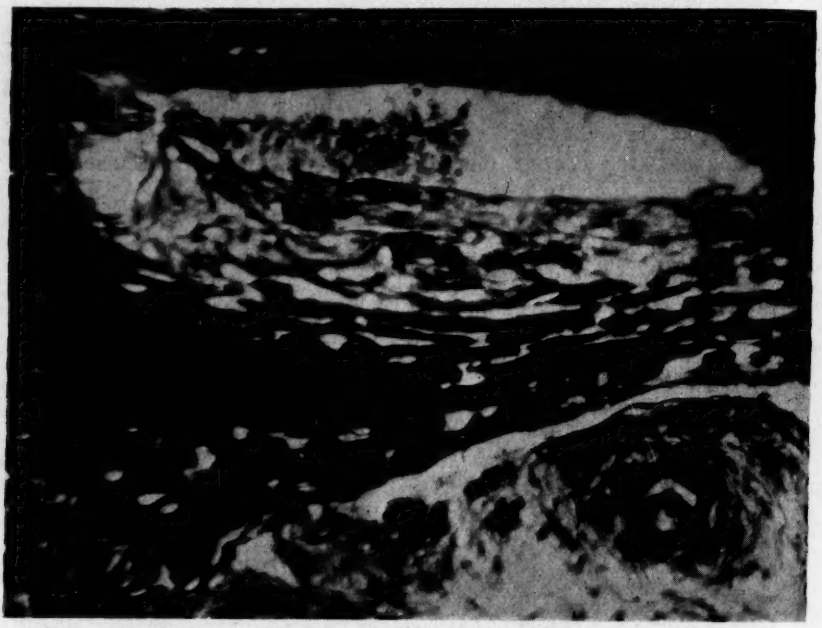

FIG. 4.—Section of canal of Schlemm. × 230. Multinuclear cap in projection of inner wall, fine fibrils beneath endothelium. The canal contains blood.

Furthermore, this inner wall is usually described as being formed by the trabeculae of the ligamentum pectinatum iridis, and, although both Salzmann (1912) and Rochon-Duvigneaud (1892) noted a different type of tissue directly under the endothelium, they were doubtless describing the appearance seen when haematoxylin and eosin or van Gieson had been used as the stain. Salzmann said the tissue resembles that under the endothelium of the outer wall of the canal, and Rochon-Duvigneaud described it as compact or dense. With Mallory's triple stain after Zenker fixation this tissue is seen to consist of a reticulum of very fine fibrils; it probably has the consistency of cotton wool, and I would suggest that it is homologous with

the tissue under the endothelium of a Pacchionian body or arachnoidal villus, that is, with the protruded arachnoid.

Deep to this are some fibres which resemble those of the main mass of the ligamentum, but are frailer and contain only an ill-defined core of *connective and elastic tissue; these no doubt represent the subarachnoid* trabeculae.

The trabeculae of the ligamentum, with their well-marked core of connective and elastic tissue, follow; they have the characteristics of scleral tissue and doubtless represent the dura through which the villus makes its way.

Thus there can be little doubt that Pacchionian-like bodies occur in the human canal of Schlemm.

SUMMARY

With Mallory's triple stain following Zenker fixation the structure of the inner wall of the canal of Schlemm in man is as follows:

The inner wall may be flat or jut in like a villus. It may even reach the outer wall. It is usually lined by a single layer of endothelium, but this may be in two or more layers and may even form a cap of nuclei like that in a Pacchionian body or arachnoidal villus. Beneath this is a layer of very fine fibrils like those beneath the endothelium of a Pacchionian body. Deep to this are trabeculae which resemble the subarachnoid trabeculae of a Pacchionian body. Then and then only come the trabeculae of the ligamentum pectinatum iridis.

My thanks are due to Dr. Peter Hansell and the medical illustration department at the Institute of Ophthalmology for the photographs.

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CASE NOTES

CONGENITAL PIGMENTATION OF THE CORNEA*

BY

EUGENE CHAN

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CONGENITAL deposits of pigment may be found in the epithelial or endothelial layer of the cornea (Duke-Elder, 1938; Berliner, 1949). In the Chinese race, the normal pigmentation of the limbus may extend a little distance beyond the limbal margin into or underneath the corneal epithelium. Melanin deposit on the endothelial layer may be associated with filaments of persistent pupillary membrane adherent to the posterior surface of the cornea. The case reported below is unique in that it does not fit into either of these two categories.

Case Report

Male, Chinese, aged 21.—He visited the out-patient department of the David Gregg Hospital in the Hackett Medical Centre on February 20, 1951, because of a tiny foreign particle on the right cornea. After removal of the foreign matter, I could see no other pathological lesion in the right eye.

Upon routine examination of the patient's left eye, I could discover no abnormality other than a triangular area of fine haze, located in the inferior third of the cornea (Fig. 1). When viewed with oblique illumination under a loupe, this nebulous area could be resolved into numerous small dots of pigment. The arrangement of the dots closely resembled that of keratic precipitates in iridocyclitis. When this area was observed by slit-lamp microscopy, the dots were seen to have approximately uniform dimensions; they assumed a golden-yellow colour and crow-foot-like appearance. Most of them lay so close together that their pseudopods touched one another. The colour, shape, and size of the dots reminded one of the congenital iris pigment occasionally perceived on the anterior lens capsule; optical section of the cornea showed them to be situated in the foremost lamellae of the corneal stroma (Fig. 2).

There was no neovascularization of the cornea. The thickness and curvature of the cornea were within normal limits. Vision in the right eye was 6/10, in the left eye 6/7.5.

Comment

The pigment dots were fortuitously observed in the left eye which had always been healthy, and had given no cause for complaint. There was no history of inflammation or trauma, nor of any drugs being instilled into the eye. No melanotic changes were found in the conjunctiva, sclera, or iris.

As far as we can judge, the pigmentary anomaly of the cornea is of congenital

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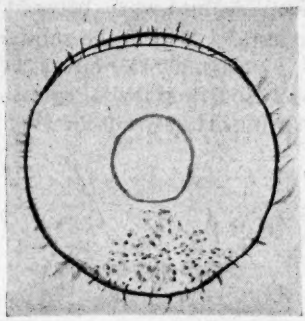

FIG. 1.—Anterior view of cornea, showing distribution of pigment.

FIG. 2.—Optical section seen with biomicroscope, showing pigment in anterior part of cornea just behind epithelial layer.

origin, and its development should be traced back to the second month of embryonic life. According to Mann (1948), in the 8-mm. human embryo (30 days), the lens vesicle, which is connected with all the surrounding cells by fibrils of the anterior and posterior mesostromal vitreous, lies in close apposition to the surface ectoderm from which it has just separated (Fig. 3).

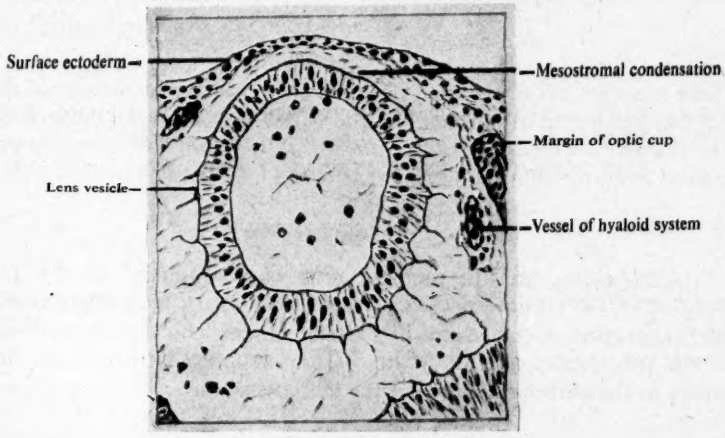

FIG. 3.—Section through 8-mm. human embryo.

The narrow space between the surface ectoderm and the lens is occupied by a mesostromal condensation, along the deep surface of which two waves of cells will grow from the reservoir of undifferentiated mesoderm lying between the lens and the margin of the optic cup. The first wave of cells will form Descemet's endothelium; the second, slightly posterior to it, will form the

stroma of the iris and the pupillary membrane. A third wave, between the mesostromal membrane and the surface ectoderm, will form the substantia propria of the cornea. By the 25-mm. stage (7 weeks), the two waves of cells which form the cornea are complete, and the mesodermal iris is represented by a very thin layer of cells lying in contact with the lens capsule (Fig. 4).

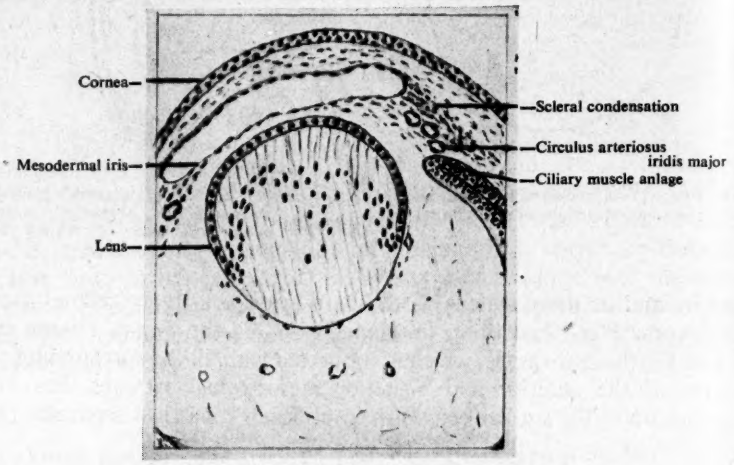

FIG. 4.—Section through 25-mm. human embryo.

There is as yet no ectodermal portion to the iris, as the margin of the optic cup has not begun to differentiate and barely reaches the equator of the lens. The pigment manifested in the cornea of our patient's left eye was evidently derived from the same source as that in the mesodermal iris.

Summary

Golden-yellow, stellate pigment dots were observed in the foremost lamellae of the corneal stroma of a patient's eye. They aggregated in the inferior portion of the cornea in a triangular configuration which resembled keratic precipitates in iridocyclitis. They apparently arose from the same source as the chromatophores of the mesodermal iris.

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MARRIAGE OF TWO COMPLETE ALBINOS WITH NORMALLY PIGMENTED OFFSPRING*

BY

P. D. TREVOR-ROPER

London

ALBINISM is a hereditary defect in melanin anabolism whose simple recessive inheritance appears to be undisputed (Duke-Elder, 1950; Sorsby, 1950; Waardenburg, 1932), so that defective children could be confidently anticipated should two albinos marry. The percentage of albinos in Scotland is about one in 21,000 and they are still rarer in England (Pearson and others, 1911), so that there is considerably less than one in a million chance of two such albinos marrying and the oculist has rare occasion to consider such a veto. Indeed, the only case on record is one among the 675 pedigrees tabled by Pearson and others (1911), and concerns two Fijian Islanders, long since dead, grandparents of an albino (also dead), who were recalled by a chief with a long memory; only two partial albino marriages (in Sierra Leone and the Phillipines) are noted, and subsequent pedigrees examined show no further case.

Case Report

Mr. and Mrs. I., both albinos, met at a partially-sighted school, married, and had three children with normal pigmentation and dark irides. There are no known albinoid relations, as shown in the accompanying pedigree (Fig. 1).

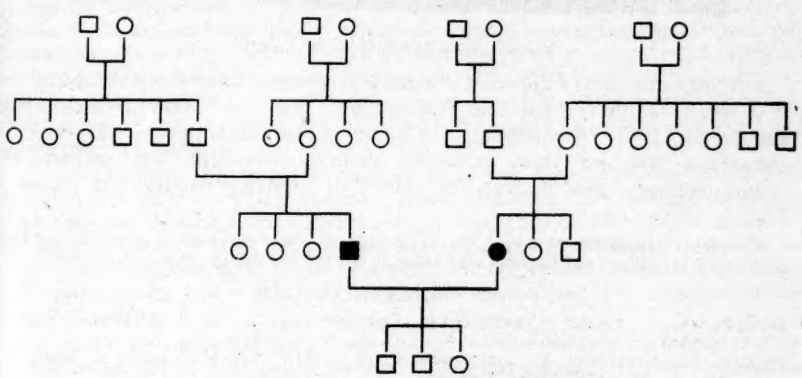

FIG. 1.—Pedigree of I. family.

* Received for publication November 12, 1951.

Mr. F. I., aged 34, generalized albino, virtually complete, although hair slightly darker than his wife's, pink translucent irides, and albinotic fundi. Vision—Right = 6/60 with +1.5 D.S., +3 D.C., 90°; Left = 4/60 with +2 D.S., +3 D.C., 90°. Alternating 50° convergent squint with paresis of both external recti and marked rotatory nystagmus.

Mrs. J. V. I., aged 31, generalized albino, complete, pink translucent irides, and albinotic fundi. Vision — Right = 4/60 with − 12 D.S., − 5 D.C. 180°; Left = 3/60 with −16 D.S. Alternating 20° divergent concomitant squint and marked rotatory nystagmus. Slight photophobia.

The first child died after a few hours but was certified by the doctor to be normally pigmented.

Fred I., aged 7, and Pamela I., aged 18 months, have normal pigmentation with dark brown irides (not translucent, as is said to occur in heterozygotes by Waardenburg), normally pigmented fundi, and negligible refractive errors. The boy has vision 6/6 in both eyes.

FIG. 2.—Four members of the I. family.

Although one case of apparent dominant inheritance among generalized albinos in a Negro family (Pipkin and Pipkin, 1942) and two doubtful cases (Pipkin and Pipkin, 1942; Waardenburg, 1932) are quoted, such open violation of the Mendelian laws on three occasions deserves comment and perhaps also congratulations. The parents and their two surviving children are shown in Fig. 2.

My acknowledgements are due to Mr. A. G. Cross at whose clinic Mr. I. attended, and to the department of medical illustration at the Institute of Ophthalmology for the photographs.

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CORRESPONDENCE

RECORDING PUPILLOGRAPH OF SIMPLE DESIGN

To the Editorial Committee of the

BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS—After the publication of our paper in your October issue (*British Journal of Ophthalmology*, **35**, 632) we found an article by J. Piltz (*Neurol. Zbl.*, 1904, **23**, 801, 853) describing an apparatus similar to that described by us.

It was of course impossible in 1904 to take full advantage of the idea; but we are eager to give the author the credit he deserves for his original conception at that early date.

Yours faithfully,

L. H. VAN DER TWEEL.

UNIVERSITY PHYSICAL LABORATORY,
AMSTERDAM.

November 21, 1951.

BOOK REVIEWS

The Glaucomas. By H. S. SUGAR. 1951. H. Kimpton, London. Pp. 469, 123 illus., bibl. (84*s.*)

It is a considerable time since a treatise on glaucoma has appeared and this book is welcome, if only in that it brings together and assesses the enormous amount of new observations which recent biochemical researches and new clinical techniques such as gonioscopy have produced. Sugar's work on glaucoma, first with the late Dr. Harry Gradle in Chicago, and then in his own clinic at Detroit, is, of course, well known, and he has become one of our contemporary authorities on gonioscopy and on the application and interpretation of the various provocative tests. The book is a small one, and does not enter into the subject exhaustively, but it gives a clear and readable outline of the whole clinical picture of the primary and secondary glaucomas as seen by one whose opinion is worth respect.

The adult primary glaucomas are classified as chronic simple glaucoma, which goes through a non-congestive and a congestive phase, and acute (narrow-angle) glaucoma, which also goes through a non-congestive and a congestive phase; it might be argued that the term " acute " may be slightly inappropriate to describe the many cases wherein minor rises of tension occur over many years without causing serious symptoms or inconveniencing the patient except for mild and transient attacks of halos and mistiness of vision.

The secondary glaucomas are discussed under various headings according as they are due to mechanical blockage of the trabecular spaces, to lack of a communication between the anterior and posterior chambers, to irritation of the ciliary body, to venous obstruction, to proliferating anastomotic vessels in the region of Schlemm's canal, to trauma, epidemic dropsy, angiomata, and, finally, to " mixed " and miscellanous causes.

The book is very informative and full of sound teaching, and gives a clear and well-integrated idea of modern thought regarding this perplexing disease. If the reviewer were to be critical at all, he might suggest that the impression received is that the subject is over-simplified and that not enough stress is laid on the immensity of our ignorance regarding many of its fundamental problems. There are also one or two points with which every ophthalmologist might not agree—for example, that an important cause of primary glaucoma is osmotic failure in the functioning of the canal of Schlemm. Sugar accepts Friedenwald's view that this canal is supplied by arterioles which convey plasma into the canal and which in glaucoma become sclerosed, that the content of Schlemm's canal is plasma, and that the aqueous veins should therefore be called plasma veins. This theory is built on a single histological observation, the interpretation of which is somewhat problematical. Moreover, the suggestion is made in several places that glaucoma may be caused by over-secretion of the aqueous humour; again, there is very little evidence to support this view. There are one or two minor mistakes, such as the statement that acetylcholine is the substance responsible for the transmission of all nerve impulses across synapses when all "sympathetic" synapses are obviously meant. But, on the whole, no one interested in the problem of glaucoma will find it possible to overlook this excellent résumé.

Systemic Ophthalmology. By ARNOLD SORSBY. 1951. Butterworth, London. Pp. 712, 309 figs. (84*s*.).

This book represents the work of some thirty collaborators, each an expert in his or her own field. The designation of "systemic" is justified by Professor Sorsby in his short preface, where he points out that the adjective "medical" has now become too narrow for the general aspects of eye disease which include surgical, obstetric, metabolic, and dermatological diseases and abnormalities, as well as other conditions. Enormous though the subject of Systemic Ophthalmology has now become, its many aspects are here adequately covered.

The book is divided into six main sections dealing successively with:

(1) Prenatal pathogenic influences.
(2) Inflammation, allergic reactions, and infections.
(3) Nutritional, metabolic, and endocrine disturbances.
(4) Central nervous system.
(5) Cardiovascular and haemopoietic systems.
(6) Other general disturbances.

These sections are sub-divided into chapters, for each of which one of the collaborators is responsible; it seems appropriate that the penultimate chapter should deal with senile changes in the eye and the last one with the eye at death. Systemic Ophthalmology thus gives a complete life history of what may happen to the eye, since the first chapter deals with concepts derived from experimental embryology.

One way of summing up one's reactions after reading this book is to adopt an Americanism and say that it constitutes a "must" so far as ophthalmic surgeons are concerned, and particularly for those who have to examine or lecture to students. Many examples could be quoted to show this, but two must suffice. The first concerns maternal rubella contracted during the first 4 months of pregnancy, which can produce, we are told, not only cataract in the offspring, but also buphthalmos and pigmentary retinal change, in addition to various systemic disturbances such as deaf-mutism, microcephaly, mental retardation, dental anomalies, and heart disease, the chances in favour of these changes occurring being 3:1. The second example concerns allergy; we all have some general conception of this condition, but the whole matter is clarified when it is divided into five main groups, and emphasis placed upon the difference between

reactions due to allergy and those due to immunity. The work of the Johns Hopkins Medical School on this subject is well known and the editor is fortunate in having Alan C. Woods as author of the chapter on Ocular Tuberculosis. This alone would justify the publication of Systemic Ophthalmology, but the other sections and chapters are also of a high standard and thus the best of recent publications in British and foreign ophthalmic journals, together with the original observations of the various contributors, are integrated into one volume.

The chapter dealing with organic affections of the central nervous system is well written and contains much useful information, *e.g.*, a list of the causes of nystagmus, which number more than seventy! The neurologists who have written the chapter, however, probably do not realize that those who read it may be less familiar with the central nervous system than they are themselves, and a few diagrams such as are to be found in anatomy books would be helpful.

Professor Sorsby and his collaborators and publishers have certainly earned the appreciation and gratitude of English-speaking ophthalmologists in producing a work which is not only useful and of good format but serves to show how wide is our specialty. Coventry Patmore once wrote—not in reference to ophthalmology:

> What in its ruddy orbit lifts the blood
> Like a perturbed moon of Uranus
> Reaching to some great world,
> In ungauged darkness hid.

Systemic Ophthalmology would seem to lift our blood out of the orbit to provide means whereby we can gauge, at any rate, some of the darkness that lies beyond it.

NOTES

MEDICAL RESEARCH COUNCIL

TRAVELLING FELLOWSHIPS IN OPHTHALMOLOGY AND OTOLOGY, 1952-53

THE Medical Research Council invite applications for Travelling Fellowships in Ophthalmology and Otology for the academic year 1952-1953, for which special provision has been made by the Alexander Pigott Wernher Memorial Trustees. Under the terms of the bequest, the funds are to be applied "towards the prevention and cure of blindness and deafness in the United Kingdom and British Empire and in particular research in connection therewith by financing medical men and students within the Empire to study methods and practices in all countries of the world".

These fellowships are intended for suitably qualified medical graduates who are likely to profit by a period of work in ophthalmology or otology at a centre abroad before taking up positions for higher teaching and research in these branches of medical science. Candidates will be required to submit an outline of their proposals for study or research and to indicate their preference as to place of work. The awards will, as a rule, be tenable for one year.

The fellowships provide for the payment of stipend, together with an allowance for travelling and incidental expenses. The stipend will ordinarily be at the rate

of £650 per annum for a single Fellow, and of £900 per annum for a married Fellow, subject to appropriate adjustment in the case of fellowships tenable at centres outside the sterling area.

Forms of application for these awards may be obtained from the Secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, with whom applications must be lodged by *March 31, 1952.*

January, 1952.

CONTACT LENS SOCIETY

At the last Council Meeting, the election of the following Officers of the Contact Lens Society was confirmed:

President - - -	G. D. McKellen.
Senior Vice-President	R. W. Stephenson.
Vice-President - -	L. Evershed-Martin.
Treasurer - - -	C. H. Keeler.
Joint Secretaries -	H. Treissman, Norman Bier.

OPHTHALMOLOGICAL SOCIETY OF NEW ZEALAND

Mr. Arthur Lister, F.R.C.S. (*London*) and Dr. H. Sjögren (*Jönköping, Sweden*) have been elected Honorary Members.

OPHTHALMOLOGICAL SOCIETY OF EGYPT

The Annual Meeting of the Ophthalmological Society of Egypt will take place at the Memorial Ophthalmic Laboratory, Giza, Egypt, on March 14 and 15, 1952, at 9 a.m. Medical practitioners, oculists or otherwise, are cordially invited. Further information may be had from the Honorary Secretary, Dr. Mohammed Bey Khalil, Dar el Hekmah, 42 Kasr el Ainy St., Cairo, Egypt.

Captain Scott Medal

Dr. N. A. Stutterheim (*Johannesburg*) has been awarded the Captain Scott Medal for outstanding work in biological science in South Africa by the South African Biological Society for his work on ocular imbalance and depth vision.

Air Commodore J. C. Neely, Consultant in Ophthalmology, R.A.F., has been appointed a C.B.E.